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(54) Title: SULFONYLUREA–GLITAZONE SYNERGISTIC COMBINATIONS FOR DIABETES

(57) Abstract

Combinations of a sulfonylurea antidiabetic agent and a glitazone antidiabetic agent are useful for treating diabetes mellitus and improving glycemic control.

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SULFONYLUREA–GLITAZONE SYNERGISTIC COMBINATIONS FOR DIABETES

FIELD OF THE INVENTION

This invention relates to combinations of antidiabetic sulfonylurea compounds with glitazone compounds, and to a method for treating diabetes employing such combinations.

BACKGROUND OF THE INVENTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, insulin resistance, and is often associated with other disorders such as obesity, hypertension, hyperlipidemia, as well as complications such as cardiovascular disease, retinopathy, neuropathy, and nephropathy. The disease is progressive in nature, and can often be controlled initially by diet alone, but generally requires treatment with drugs such as sulfonylureas and injections of exogenous insulin. A new class of compounds known as the glitazones has recently received a great deal of attention for their ability to treat diabetes. These compounds operate by increasing the sensitivity of insulin receptors throughout the body, thereby diminishing or eliminating the need for exogenous insulin.

It has now been discovered that combination therapy with a sulfonylurea and a glitazone results in dramatic improvement in glycemic control. Accordingly, such combinations are especially useful in treating diabetes and associated complications.

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SUMMARY OF THE INVENTION

This invention provides a method of treating
diabetes by administering to a subject in need of
treatment a combination of a sulfonylurea antidiabetic
agent and an antidiabetic glitazone.

The sulfonylureas are a class of compounds that
have been widely employed to treat diabetes. Such
compounds are well known, for example as described in
United States Patent No. 3,454,635, 3,669,966,
2,968,158, 3,501,495, 3,708,486, 3,668,215, 3,654,357,
and 3,097,242. Most of the sulfonylurea antidiabetics
are defined by the formula

$$A \!-\!\!\!\!\bigcirc\!\!\!\!- SO_2NHCNH\!-\!B$$
$$\overset{O}{\overset{\|}{}}$$
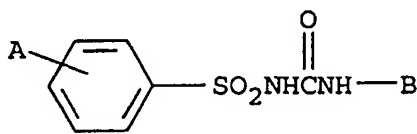
where A is hydrogen, halo, or an organic radical such
as alkyl, alkanoyl, aryl, aralkyl, heteroaryl, and
cycloalkyl, and B is alkyl, cycloalkyl, and a
heterocyclic group such as hexahydroazepine. Preferred
sulfonylureas to be employed are those wherein A is
chloro, alkyl such as methyl, or alkyl substituted with
aryl carbonyl or aryl carboxamido, for instance
3-chloro-5-methoxybenzoylethyl or 5-methyl-2-
pyrazinylcarbonylaminoethyl.

Especially preferred sulfonylureas to be employed
in the combinations of this invention are glyburide,
gliquidone, glipizide, tolbutamide, tolazamide,
glisoxepid, chlorpropamide, glibornuride, gliclazide,
glimepiride, phenbutamide, and tolcyclamide.

According to this invention, the foregoing
sulfonylureas are used in combination with a glitazone
to treat diabetes and to improve glycemic control. The
glitazones are a family of antidiabetic agents

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characterized as being thiazolidinediones or related analogs. They are described in Current Pharmaceutical Design, 1996;2:85-101. Typical glitazones have the formula

$$E-(CH_2)_n-O-\text{C}_6\text{H}_4-CH_2-\text{(thiazolidinedione, Y, NH, S, Z)}$$
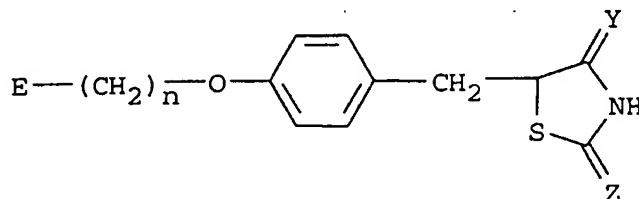
where n is 1, 2, or 3, Y and Z independently are O or NH; and E is a cyclic or bicyclic aromatic or non-aromatic ring, optionally containing a heteroatom selected from oxygen or nitrogen.

    Preferred glitazones have the formula

$$\text{(chroman ring with }R^5, R^1, R^4, R^3O, R^2, W, O\text{)}-(CH_2)_n-O-\text{C}_6\text{H}_4-CH_2-\text{(thiazolidinedione, Y, NH, S, Z)}$$
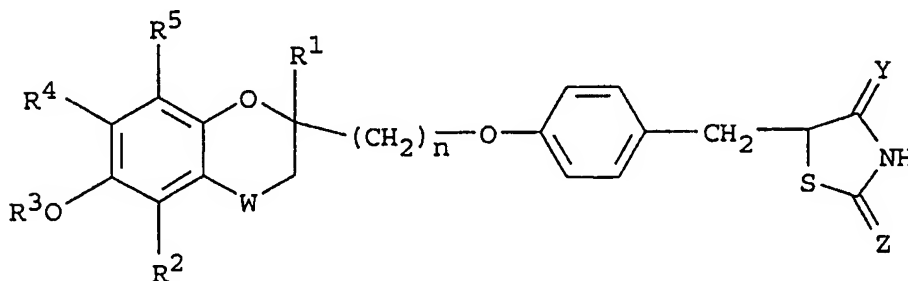
wherein:

R^1 and R^2 independently are hydrogen or C_1-C_5 alkyl;

R^3 is hydrogen, a C_1-C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1-C_6 alkoxy) carbonyl group, or an aralkyloxycarbonyl group;

R^4 and R^5 independently are hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, or R^4 and R^5 together are C_1-C_4 alkylenedioxy;

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W is $-CH_2-$, $>CO$, or $CHOR^6$, where R^6 is any one of the
atoms or groups defined for R^3 and may be the same
as or different from R^3;

n, Ẏ, and Z are as defined above, and pharmaceutically
acceptable salts thereof.

An especially preferred glitazone is troglitazone
having the formula
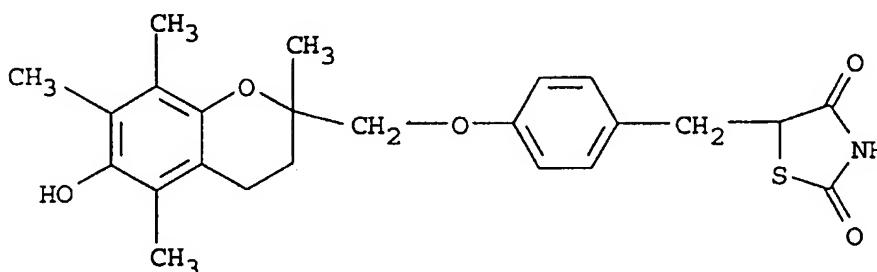
Other glitazones that can be employed in this
invention are described in United States Patent
Nos. 5,457,109 and 5,478,852, which are incorporated
herein by reference. Other specific glitazones which
are preferred include ciglitazone, pioglitazone,
englitazone, TA 174, which has the formula
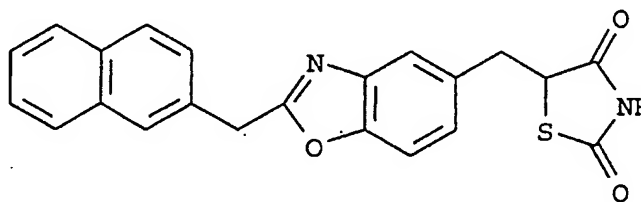
and BRL 49653 (rosiglitazone), which has the formula
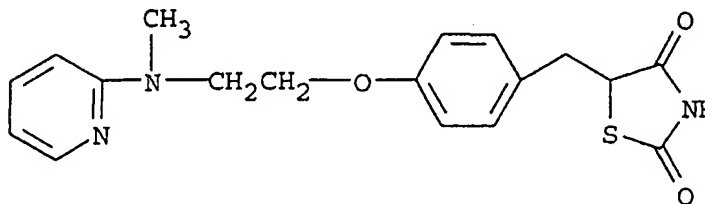
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Additionally preferred glitazones include:

5-(4-[2-[1-(4-2'-Pyridylphenyl)ethylidene-aminooxy]ethoxy]benzyl]thiazolidine-2,4-dione;

5-(4-[5-Methoxy-3-methylimidazo[5,4-b]pyridin-2-yl-methoxy)benzyl]thiazolidine-2,4-dione, or its hydrochloride;

5-[4-(6-Methoxy-1-methylbenzimidazol-2-yl-methoxy)benzyl]thiazolidine-2,4-dione;

5-[4-(1-Methylbenzimidazol-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione; and

5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the design of the clinical study used to establish the method of this invention and the typical medications administered to the individual study groups.

Figure 2 shows the change in fasting serum glucose (FSG) in mg/dL at Week 52 for each treatment group, and shows the dramatic reduction in FSG achieved with combination therapy according to this invention when evaluated by the insulin tolerance test (ITT).

Figure 3 shows the percentage change in hemoglobin A_{1c} (HbA_{1c}) in each treatment group at Week 52, and shows the dramatic reduction in HbA_{1c} effected by combination therapy.

Figure 4 shows the mean levels of FSG and HbA_{1c} for each treatment group at various time intervals over the 52-week treatment period, and demonstrates that the majority of improvement in glycemic control (FSG) was achieved by the fourth week of combination therapy.

Figure 5 shows the percentage distribution of patients in each treatment group with HbA_{1c} levels less

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than or equal to 8% at baseline and at 52 weeks of
treatment, and establishes the synergistic increase in
control achieved with combination therapy.

DETAILED DESCRIPTION OF THE INVENTION

According to this invention, a sulfonylurea is
used in combination with a glitazone to treat diabetes
and to improve glycemic control in patients in need of
treatment. The compounds can be employed individually
or can be combined in a single formulation, for example
as a tablet, capsule, syrup, solution, as well as
controlled release formulations. In a preferred
embodiment, the sulfonylurea and glitazone are
formulated individually and administered in the same
manner that each is normally used clinically.

The dosage of each agent will vary depending upon
the severity of the disease, the frequency of
administration, the particular agents and combinations
utilized, and other factors routinely considered by an
attending medical practitioner. The sulfonylurea
normally will be administered at a daily dose of from
about 0.25 mg to about 500 mg, typically about 3 mg to
about 250 mg. A typical dosage for glyburide, for
example, will be about 10 to about 20 mg per day. The
glitazones will normally be administered at doses from
about 5 mg to about 2500 mg per day, and more typically
from about 50 mg to about 1500 mg per day. A preferred
glitazone is troglitazone, and it will be employed at
doses from about 100 mg to about 1000 mg per day.

The invention provides compositions of a
sulfonylurea and a glitazone, and a method of treating
diabetes and controlling glycemic conditions comprising
administering to a patient in need of treatment an
effective amount of a sulfonylurea and an effective

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amount of a glitazone. When the sulfonylurea and
glitazone are formulated together, the compositions
will contain about one to about 1000 parts by weight of
sulfonylurea, and about 1000 to about one part by

5   weight glitazone. For example, a typical composition
of glyburide and troglitazone will contain about 12 mg
of glyburide and about 500 mg of troglitazone. Such
combination will be administered to an adult patient
about once each day to achieve a synergistic glycemic

10   control.

       The compositions may contain common excipients and
carriers such as starch, sucrose, talc, gelatin,
methylcellulose, and magnesium stearate. The
compositions will normally be made for oral

15   administration, for instance as tablets or capsules,
but also may be in the form of aqueous suspensions or
solutions, suppositories, slow release forms, for
example employing an osmotic pump, skin patch, or the
like.

20   The method of treating diabetes employing a
combination of a sulfonylurea and a glitazone has been
established in a long-term controlled clinical
evaluation. The study determined the efficacy and
safety of troglitazone alone and in combination with

25   the sulfonylurea glyburide for the treatment of non-
insulin dependent diabetes mellitus (NIDDM). This
study targeted the segment of the NIDDM population in
which the disease state has progressed to a point where
maximum doses of sulfonylureas no longer produce

30   adequate glycemic control. These patients are at a
stage where the maximally stimulated pancreatic insulin
secretion does not keep up with the increasing demand.
Since the unstimulated (absence of sulfonylurea)
insulin secretory capacity of the beta cells is very

35   low in this population, reversing insulin resistance
alone would be of partial benefit. Therefore,

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maintaining a level of stimulated insulin secretion
with a sulfonylurea while adding troglitazone to
improve insulin sensitivity could provide a level of
glycemic control unattainable by either medication
5   alone.

A primary objective of the study was to assess the
efficacy of troglitazone alone or in combination with
micronized glyburide in patients with NIDDM by
comparing changes in markers of glycemic and lipid
10 homeostasis over 1 year of treatment. Long-term safety
was also an objective of this study, assessed by
adverse events and clinical laboratory data.

The effect of treatment on the pattern of
postprandial glucose tolerance (standard 2-hour meal
15 tolerance test) was determined in a subset of patients.
In addition, heart mass and function (echocardiographic
procedure) were monitored in a subset of patients.

Thirty centers in the US (Table 1), each with
matching protocol and case report forms, participated
20 in this study. This study was conducted according to
Good Clinical Practices Guidelines. Institutional
Review Board approval and informed patient consent were
obtained prior to the study.

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TABLE 1. List of Investigators

Center 991-55-	State	Number of Patients	
		Randomized	Completed
01	Louisiana	20	7
02	Indiana	27	16
03	Illinois	14	9
04[a]	New York	30	18
05	Georgia	21	9
06[b]	Texas	22	11
07[b]	Louisiana	8	8
08	Massachusetts	12	5
09[b]	Missouri	11	5
10	North Carolina	19	4
11	Wisconsin	23	13
12	Florida	29	20
13	Colorado	19	15
14[b]	California	11	9
15	Ohio	14	11
16[b]	Michigan	6	3
18[b]	Nebraska	27	18
20	California	18	7
21	Texas	26	16
22	Massachusetts	13	2
23	California	10	7
24	Colorado	15	11
25	Colorado	32	13
26	Nebraska	35	22
27	Wyoming	11	8
28	California	23	16
29[b]	Michigan	15	9
30	Alabama	9	5
31	Missouri	25	15
32	Michigan	7	6
Total		552	318

[a] Meal tolerance testing performed at this site.
[b] Meal tolerance and echocardiograms performed at this site.

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Corning Nichols Institute was contracted to provide all testing of blood and urine samples for efficacy and safety results. Corning Hazelton (Madison, Wisconsin) supplied all troglitazone plasma assay results.

This was a 12-month, double-blind, randomized, parallel-group, active-control, multicenter study design (Figure 1).

After an initial screening visit, patients meeting the inclusion criteria entered a 4-week baseline phase (unblinded) in which they received 12 mg micronized glyburide (6 mg BID). At the end of the baseline phase, patients who still exhibited a fasting serum glucose (FSG) of >140 mg/dL and <300 mg/dL were randomized to 1 of 7 blinded parallel treatment arms. Treatment consisted of troglitazone monotherapy, troglitazone/glyburide combination therapy, or glyburide monotherapy (active control).

Troglitazone was supplied in the form of 200-mg tablets (Table 2). Matching glyburide tablets were also supplied to maintain blinding.

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TABLE 2.   Lot/Formulation Numbers for
Study   Medications

Study Medication	Lot	Formulation
Troglitazone 200-mg Tablet	CM 0120295	137070-13
	CM 1581194	137070-13
Glynase (Glyburide)		
3-mg Prestab Tablet	202JP	marketed[a]
	944JD	marketed[a]
3-mg Tablet in Capsule	CM 0010195	137070-11
	CM 0560595	137070-11
	CM 0900694	137070-11
	CM 1491194	137070-11
Placebo		
Tablet (Troglitazone Match)	CM 0200295	137070-8P
	CM 0780594	137070-8P
Capsule (Glynase Match)	CM 1030694	14964-2PAM2
	CM 1481194	14964-2PAM2

[a] Used in production of 3-mg capsule

Patient Selection

<u>Inclusion Criteria</u>

Men or women greater than 18 years of age with
NIDDM (National Diabetes Data Group criteria), a
fasting C-peptide level of ≥ 1.5 ng/mL, FSG >140 mg/dL,
and hemoglobin A_{1c} (HbA$_{1c}$) levels greater than the
normal range (>5.9%) were selected for the study.
Patients were also required to have been receiving
maximum doses of a sulfonylurea to qualify as a
sulfonylurea failure.

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Exclusion Criteria

Patients were excluded from the study if they had
used insulin (chronically) or had a history of
ketoacidosis, symptomatic diabetic neuropathy or
5   retinopathy, or renal disease. Patients were also
excluded from the study if they were of childbearing
potential, had angina pectoris, congestive heart
failure (Class III or IV), significant hypertension, a
major vascular medical event within 3 months of the
10   study, significant hepatic enzyme elevation, anemia,
active cancer within 5 years of the study, or received
another investigational drug within 1 month of
screening.

15   Prohibited Medications

No medications were specifically prohibited for
concurrent use except beta blockers, which block the
acute adrenergic symptoms (the early warnings) of
hypoglycemia. Previous oral antidiabetic medications
20   were discontinued upon completion of screening and
start of the baseline phase.

Dosage levels of all concurrent medications were,
if medically appropriate, to remain unchanged while the
patient was enrolled in the study. Of particular
25   interest were thiazide diuretics, steroids, oral
contraceptives, and calcium channel blockers, which are
known to counteract the actions of sulfonylureas.

The use of insulin was prohibited except for
emergency care for a period that was not to exceed
30   3 consecutive days.

Guidelines for Patient Withdrawal

Patients could withdraw voluntarily at any time
during the study or be withdrawn by the investigator
35   because of significant adverse events or deterioration
in health, poor compliance, pregnancy, or prolonged

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symptomatic hyperglycemia or persistent worsening or
failure to improve glycemic control as monitored by
FSG. Patients who required emergency insulin use
longer than 3 consecutive days were to be removed from
5   the study.

Evaluations

Efficacy

10   The primary efficacy parameters included endpoints
related to glucose homeostasis: FSG and HbA_{1c}. The
change from baseline in these parameters at Week 52
compared to active control (glyburide) was the primary
measure of efficacy. For patients terminating early
15   from the study, their last observation was carried
forward (LOCF) to Week 52. A decrease in these
parameters was indicative of an improvement in glycemic
control.
      Secondary efficacy parameters included markers of
20   glycemic homeostasis (insulin and C-peptide) and
markers of lipid metabolism (total cholesterol, total
triglycerides, HDL, VLDL, LDL (measured), free fatty
acids, Lp(a), Apo A1, and Apo B).
      The following sets of treatment comparisons were
25   considered **primary**:
      • Comparison of each troglitazone/glyburide
        combination group with the glyburide-monotherapy
        group.
      • Comparison of each troglitazone-monotherapy group
30   with the glyburide-monotherapy group.
      The following sets of treatment comparisons were
considered **secondary**:
      • Comparison of each troglitazone monotherapy group
        with the corresponding troglitazone/glyburide
35   combination group.

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- Pairwise comparisons of troglitazone monotherapy groups.
- Pairwise comparisons of troglitazone/glyburide combination groups.

A 2-hour meal tolerance test to assess postprandial glucose and insulin excursions in response to a premeasured meal (breakfast) was conducted in a subset of patients at baseline, Week 24, and at the end of treatment. The change from baseline in the area under the glucose concentration-time curve [AUC(0-2 hr)] compared with that for glyburide was assessed. Additional parameters included total insulin and C-peptide. Analyses of the meal tolerance parameters were based on observations at the end of treatment; observations from Week 24 were not carried forward.

Pharmacokinetics

Trough plasma concentrations of troglitazone were determined at Week 12. Blood samples (7 mL) were collected in heparinized glass tubes. Following centrifugation, plasma samples were transferred to plastic tubes and stored at -20°C until assayed.

Plasma samples were assayed at Corning Hazleton, Inc., PO Box 7545, Madison, WI, 53707, using a validated liquid chromatographic method with electrochemical detection. The minimum quantitation limit for troglitazone was 5 ng/mL. Concentrations below the limit of quantitation were reported as zero. The analysts remained blinded to the treatment randomization code during sample analysis.

Mean and percent relative standard deviation (%RSD) values of trough troglitazone concentrations were calculated for each treatment group using SAS 6.08.

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Quality of Life (QOL) Assessments

QOL was assessed by a self-administered questionnaire designed to assess health status, as perceived by the patient, just prior to treatment and at Weeks 12, 24, and 52. The questionnaire consisted of the SF-36 Health Survey and a Diabetes-Related Symptoms section.

Safety

A complete physical examination and ECG were performed during screening and at the end of the study. Clinical laboratory parameters and vital signs including blood pressure were monitored throughout the study for safety reasons. Adverse events were recorded during clinic visits and evaluated by the investigator for intensity and relationship to study drug. Reduction in the daily dose of micronized glyburide could occur in cases of documented hypoglycemia.

The effect of troglitazone treatment on heart mass and function was assessed in a subset of patients by measuring left ventricular mass index (LVMI), cardiac index (CI), stroke volume index (SVI), and peripheral resistance (R) at baseline and following 6 and 12 months of treatment. Analyses of cardiac function are based on data at the study end point; observations from Month 6 were not carried forward.

All patients randomized to treatment were included in all safety evaluations.

Clinical Observations and Laboratory Measurements

The schedule of study visits and procedures is presented in Table 3. Patients were instructed to fast overnight prior to visits requiring specimen collection.

TABLE 3.   Timetable and Visit Procedures
(Page 1 of 2)

Phase	Screening		Baseline	
Length (Week)	1		4	
Week	-5	-4	-2	-1
Medical History	X			
Physical Exam		X		
12-Lead ECG		X	X	
Diet Instruction/Assessment		X	X	
Weight, Pulse, Blood Pressure	X	X	X	
Concurrent Med Query and AE Query	X	X	X	X
Diabetic Symptoms Assessment	X	X	X	X
Laboratory Panel (Safety Parameters)[a]	X	X	X	X
Laboratory Panel (Glycemic Indicators)[c]	X	X	X	X
Laboratory Panel (Lipid Indicators 1)[d]		X		X
Laboratory Panel (Lipid Indicators 2)[e]				X
Discontinue Prior Antidiabetic Drug		X		
Dispense Study Drug		X	X	
Verify Patient Compliance			X	
Quality of Life Questionnaire				

[a] Safety parameters are listed in Appendix X.
[b] Sample for Drug Level Analysis also.
[c] Glycemic indicators included FSG, HbA_{1c}, insulin, C-peptide.
[d] Lipid Indicator 1 included total cholesterol, triglycerides, free fatty acids, LDL (measured), HDL, and VLDL (Beta Quant)
[e] Lipid Indicator 2 included Apo A1, Apo B, and Lp(a).

TABLE 3. Timetable and Visit Procedures
(Page 2 of 2)

Phase	Active Treatment 52 Weeks													
Length (Week)														
Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Medical History	X													
Physical Exam														X
12-Lead ECG														X
Diet Instruction/Assessment														
Weight, Pulse, Blood Pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent Med Query and AE Query	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diabetic Symptoms Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Panel (Safety Parameters)[a]	X	X	X	X[b]	X	X	X	X	X	X	X	X	X	X
Laboratory Panel (Glycemic Indicators)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Panel (Lipid Indicators 1)[d]	X	X	X	X			X				X			X
Laboratory Panel (Lipid Indicators 2)[e]	X					X	X						X	X
Discontinue Prior Antidiabetic Drug	X													
Dispense Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	
Verify Patient Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaire	X			X			X							X

[a] Safety parameters are listed in Appendix X.
[b] Sample for Drug Level Analysis also.
[c] Glycemic indicators included FSG, HbA_{1c}, insulin, C-peptide.
[d] Lipid Indicator 1 included total cholesterol, triglycerides, free fatty acids, LDL (measured), HDL, and VLDL (Beta Quant).
[e] Lipid Indicator 2 included Apo A1, Apo B, and Lp(a).

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Data Evaluability

Efficacy analysis was performed on 2 patient
populations, *intent-to-treat* and *completers*. The
intent-to-treat comprised all patients randomized to
5   treatment who had a baseline measurement and at least
one follow-up measurement taken after randomization.
Patients withdrawing from the study before Week 52 were
included in the analysis using the LOCF procedure; the
last measurement on treatment was substituted for the
10   missing Week 52 measurement. The intent-to-treat
patient sample was the primary sample for assessing
efficacy. Completers comprised patients in the intent-
to-treat sample who completed Week 52.

Safety analysis was performed on all patients
15   randomized to treatment.

Statistical Methods

Efficacy Analysis

20   The analysis of change from baseline to Week 52
was performed using analysis of covariance (ANCOVA).
The primary model included effects due to treatment and
center and baseline as covariate. Treatment-by-
baseline and treatment-by-center interactions were also
25   examined in supplemental models.

* For the primary comparisons of glyburide versus
    each combination, step-down tests for linear trend
    in dose response were performed based on the
30   primary model.

* For the remaining primary pairwise comparisons of
    glyburide versus each monotherapy, t-tests were
    performed using the MSE from the analysis of
35   covariance (with a Bonferroni-Holm adjustment).

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For all comparisons with glyburide, 95% confidence
intervals are provided using Dunnett's test.

All tests were 2-sided and conducted at $\alpha = 0.05$.
The level of significance for the primary treatment
5   comparisons was adjusted for multiplicity. The
adjustment was performed within each set of primary
treatment comparisons. The level of significance was
not adjusted for the secondary treatment comparisons.

10   *Primary Efficacy Parameters*

Summary statistics for baseline, follow-up (post-
randomization), and change from baseline in HbA_{1c} and
FSG were computed by treatment group and visit. For
each patient, the baseline measurement for a given
15   parameter was defined as the measurement at Week 0.

The effect of baseline covariates such as age,
gender, race, body mass index, and duration of diabetes
was investigated.

20   *Secondary Efficacy Parameters*

*Fasting Lipid Parameters, C-Peptide, Insulin, and Blood
Pressure*

Summary statistics for baseline, follow-up (post-
25   randomization), and change from baseline in secondary
efficacy parameters were computed by treatment group
and visit. For each patient, the baseline measurements
for insulin, C-peptide, blood pressure, total
cholesterol, triglycerides, LDL, HDL, VLDL, and free
30   fatty acids were defined as the measurement at Week 0.
In order to reduce variability, the baseline Apo A,
Apo B, and Lp(a) levels were defined as the average of
the respective measurements at Weeks -1 and 1.
Similarly, the end-of-treatment Apo A, Apo B, and Lp(a)
35   measurements were defined as the average of the
respective measurements at Weeks 48 and 52. Averages

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from Weeks 20 and 24 were not carried forward for these
special lipid parameters.

Hemoglobin A_{1c} and Glucose Responders

Patients achieving at least a 1% absolute
reduction from baseline in hemoglobin A_{1c} were defined
as responders. The frequency distribution (number and
percentage) of responders were provided by treatment
group and visit. For the set of primary treatment
comparisons concerning glyburide versus combination
therapy, step-down comparisons of responders in each
treatment group versus the glyburide group were
performed by sequential application of the Cochran-
Mantel-Haenszel (CMH) test for linear trend with study
centers as strata. Primary comparisons of glyburide
versus troglitazone monotherapy were conducted using
the CMH test for general association with a Bonferroni-
Holm adjustment for the 3 comparisons. The CMH test
for general association were also used to perform the
secondary treatment comparisons as supplemental
analysis.

A similar analysis was performed on glucose
responders defined as patients with at least a 30 mg/dL
reduction in fasting glucose from baseline.

Meal Tolerance

Summary statistics for glucose, insulin, and
C-peptide levels every 30 minutes for 2 hours were
provided at baseline, and Months 6 and 12. The
following response variables were analyzed: the area
under the curve (AUC) of the changes from baseline from
0 to 2 hours, the change from baseline in the above
parameters at 2 hours, and tmax for insulin at baseline
and Month 12.

The change from baseline in each response variable
was compared between treatment groups using analysis of

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covariance. The analysis included all patients who had
baseline and Month 12 test data. The primary model
included effects due to treatment and center and
baseline as covariate. The 95% confidence interval for
the treatment difference based on the primary model was
provided for each pairwise comparison of treatment
groups.

Safety Analysis

Medical history, physical examination, vital
signs, biochemical parameters, electrocardiograms, and
adverse events were summarized.

Summary statistics were provided for cardiac mass
and function parameters (LVMI and CI). For each
parameter, the 95% confidence interval for the
difference between each treatment group and the
glyburide group in mean change from baseline was
developed. The analysis at Month 12 was performed
using *completer* patients.

Although troglitazone monotherapy has not caused
hypoglycemia in patients studied to date, combination
therapy or glyburide monotherapy may potentially result
in hypoglycemia. Hypoglycemia, defined as an FSG
<50 mg/dL (verified laboratory value), was to be
recorded as an adverse event.

PATIENT DEMOGRAPHICS, TREATMENT, AND DISPOSITION

Characteristics of Total Patient Sample

Characteristics of all patients randomized to
treatment are summarized in Table 4; overall, 40% of
the patients were women and 26% were ≥65 years of age
(mean age 58 years). Patients were evenly distributed
across treatment groups with respect to sex and race.
Mean age, duration of diabetes, and body mass index
(BMI) were also similar across treatments. The mean

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BMI of 32 mg/kg^2 indicates that, in general, the patients were obese. Overall, the mean duration of diabetes was greater than 8 years; mean FSG was 224 mg/dL and mean HbA$_{1c}$ was 9.6%, indicating that these patients were generally in poor glycemic control at baseline.

Approximately one-third of the patients had a mother or a father who also had diabetes. There was also a high incidence of macrovascular complications in family members, such as heart attack, stroke, and congestive heart failure.

TABLE 4. Patient Characteristics at Baseline - All Patients
(Page 1 of 4)

	Troglitazone Monotherapy		
	200 mg N = 78	400 mg N =81	600 mg N = 78
Sex, N (%)			
Men	40 (51.3)	43 (53.1)	48 (61.5)
Women	38 (48.7)	38 (46.9)	30 (38.5)
Postmenopausal	29 (37.2)	31 (38.3)	22 (28.2)
Age, yr			
Mean (SD)	58.5 (10.4)	58.9 (10.6)	56.4 (10.2)
Median	60.5	61.0	58.5
Min, Max	35.0, 75.0	32.0, 91.0	35.0, 76.0
<65 years, N (%)	52 (66.7)	61 (75.3)	61 (78.2)
≥65 years, N (%)	26 (33.3)	20 (24.7)	17 (21.8)
Race, N (%)			
White/Caucasian	63 (80.8)	64 (79.0)	59 (75.6)
Black	5 (6.4)	6 (7.4)	4 (5.1)
Hispanic	10 (12.8)	11 (13.6)	11 (14.1)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Native American	0 (0.0)	0 (0.0)	2 (2.6)
Other	0 (0.0)	0 (0.0)	2 (2.6)
Duration of Diabetes, yr			
Mean (SD)	8.6 (5.7)	8.8 (7.8)	7.7 (5.5)
Median	8.0	7.0	6.0
Min, Max	<1, 27.0	<1, 40.0	1.0, 30.0
Body Mass Index (BMI), kg/m²			
Mean (SD)	32.7 (6.7)	34.0 (7.9)	32.3 (7.1)
Median	30.5	33.0	30.5
Min, Max	22.2, 53.8	20.6, 58.4	20.5, 54.5

SD = Standard deviation

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TABLE 4. Patient Characteristics at Baseline - All Patients
(Page 2 of 4)

	Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy N = 79	Grand Total N = 552
	200 mg/12 mg N = 78	400 mg/12 mg N = 76	600 mg/12 mg N = 82		
Sex, N (%)					
Men	54 (69.2)	50 (65.8)	49 (59.8)	49 (62.0)	333 (60.3)
Women	24 (30.8)	26 (34.2)	33 (40.2)	30 (38.0)	219 (39.7)
Postmenopausal	19 (24.4)	17 (22.4)	22 (26.8)	27 (34.2)	167 (30.3)
Age, yr					
Mean (SD)	56.9 (10.4)	57.1 (10.2)	56.3 (11.6)	58.7 (10.8)	57.5 (10.6)
Median	56.0	57.5	56.5	59.0	58.0
Min, Max	28.0, 80.0	30.0, 76.0	32.0, 87.0	33.0, 87.0	28.0, 91.0
<65 years, N (%)	59 (75.6)	56 (73.7)	64 (78.0)	56 (70.9)	409 (74.1)
≥65 years, N (%)	19 (24.4)	20 (26.3)	18 (22.0)	23 (29.1)	143 (25.9)
Race, N (%)					
White/Caucasian	54 (69.2)	62 (81.6)	61 (74.4)	61 (77.2)	424 (76.8)
Black	11 (14.1)	4 (5.3)	5 (6.1)	5 (6.3)	40 (7.2)
Hispanic	12 (15.4)	9 (11.8)	14 (17.1)	12 (15.2)	79 (14.3)
Asian	1 (1.3)	1 (1.3)	1 (1.2)	0 (0.0)	3 (0.5)
Native American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Other	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.3)	4 (0.7)
Duration of Diabetes, yr					
Mean (SD)	8.7 (6.1)	8.7 (5.9)	7.7 (6.1)	9.0 (8.4)	8.4 (6.6)
Median	7.0	7.0	5.5	7.0	7.0
Min, Max	1.0, 30.0	<1, 31.0	1.0, 39.0	1.0, 57.0	<1, 57.0
Body Mass Index (BMI), kg/m^2					
Mean (SD)	31.3 (5.0)	31.2 (5.7)	31.5 (6.9)	31.9 (6.1)	32.1 (6.6)
Median	30.2	29.8	30.1	31.1	30.5
Min, Max	21.3, 47.5	21.2, 48.4	21.7, 58.9	23.5, 54.4	20.5, 58.9

SD = Standard deviation

TABLE 4. Patient Characteristics at Baseline - All Patients
(Page 3 of 4)

	Troglitazone Monotherapy		
	200 mg N = 78	400 mg N = 81	600 mg N = 78
Waist-Hip Ratio, CM			
Means (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Median	0.9	1.0	1.0
Min, Max	0.8, 1.2	0.8, 1.3	0.8, 1.2
Weight, lb			
Mean (SD)	202 (41.2)	218 (53.1)	207 (45.8)
Median	194	214	201
Min, Max	133, 292	121, 380	127, 312
FSG, mg/dL			
Mean (SD)	226.3 (45.5)	214.1 (50.1)	229.8 (48.6)
Median	228.5	221.0	219.0
Min, Max	124, 324	97, 321	115, 358
HbA$_{1c}$, %			
Mean (SD)	9.5 (1.4)	9.4 (1.4)	9.7 (1.7)
Median	9.5	9.5	9.8
Min, Max	6.4, 12.9	6.3, 13.4	5.7, 13.4
Total Insulin, µIU, mL			
Mean (SD)	32.3 (30.6)	32.7 (18.2)	30.3 (17.5)
Median	26.2	27.8	22.3
Min, Max	8.1, 264	8.9, 110	9.4, 101
C-Peptide, ng/mL			
Mean (SD)	2.9 (1.1)	3.1 (1.2)	3.0 (1.2)
Median	2.8	2.9	2.9
Min, Max	1.1, 9.0	1.1, 7.1	1.4, 8.4

SD = Standard deviation.

TABLE 4.   Patient Characteristics at Baseline - All Patients
(Page 4 of 4)

	Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy N = 79	Grand Total N = 552
	200 mg/12 mg N = 78	400 mg/12 mg N = 76	600 mg/12 mg N = 82		
Waist-Hip Ratio, CM					
Means (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Median	1.0	1.0	1.0	0.9	1.0
Min, Max	0.8, 1.1	0.8, 1.1	0.8, 1.1	0.8, 1.5	0.8, 1.5
Weight, lb					
Mean (SD)	204 (37.4)	201 (43.1)	198 (44.7)	206 (49.1)	205 (45.4)
Median	206	194	191	199	199
Min, Max	105, 312	102, 324	115, 327	124, 389	102, 389
FSG, mg/dL					
Mean (SD)	225.7 (51.0)	230.9 (42.6)	220.2 (51.0)	222.2 (41.2)	224.0 (47.4)
Median	223.0	234.0	217.5	224.0	225.0
Min, Max	126, 443	146, 329	120, 338	141, 319	97, 443
HbA1c, %					
Mean (SD)	9.5 (1.3)	9.7 (1.3)	9.4 (1.5)	9.6 (1.2)	9.6 (1.4)
Median	9.5	9.8	9.5	9.7	9.6
Min, Max	6.2, 12.4	6.2, 12.5	5.9, 13.0	6.6, 12.4	5.7, 13.4
Total Insulin, µIU, mL					
Mean (SD)	28.2 (13.3)	24.8 (10.6)	26.7 (13.9)	27.3 (14.2)	28.9 (18.1)
Median	25.0	23.9	22.6	25.8	25.1
Min, Max	8.8, 72.0	5.8, 51.7	6.3, 80.7	6.8, 72.0	5.8, 264
C-Peptide, ng/mL					
Mean (SD)	2.8 (1.1)	2.6 (0.9)	2.9 (1.1)	2.7 (0.9)	2.8 (1.1)
Median	2.6	2.5	2.8	2.6	2.7
Min, Max	0.9, 6.5	1.0, 6.8	1.2, 8.2	0.8, 4.4	0.8, 9.0

SD = Standard deviation.

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Extent of Exposure

<u>Study Medications</u>

Table 5 summarizes patient exposure to study
medication. Twenty-eight to 46% of patients completed
52 weeks of troglitazone monotherapy; 71% to 85% of
patients completed 52 weeks of combination therapy.
Greater than (or equal to) 92% of patients were
compliant throughout the study (based on investigators
assessment of compliance).

TABLE 5.　Duration of Exposure to Study Medication
[Number (%) of Patients]
(Page 1 of 2)

	Troglitazone Monotherapy		
Completed at Least[a]	200 mg N = 78	400 mg N =81	600 mg N = 78
1 Dose	78 (100)	81 (100)	78 (100)
4 Weeks	78 (100)	81 (100)	78 (100)
8 Weeks	69 (88.5)	67 (82.7)	72 (92.3)
12 Weeks	52 (66.7)	61 (75.3)	66 (84.6)
24 Weeks	38 (48.7)	44 (54.3)	48 (61.5)
36 Weeks	25 (32.1)	39 (48.1)	38 (48.7)
52 Weeks	22 (28.2)	37 (45.7)	34 (43.6)
Summary of Exposure, Weeks			
Mean (SD)	26 (19)	31 (22)	33 (19)
Median (Min, Max)	21 (1,57)	25 (1,60)	27 (1,59)

[a] Study weeks defined in Appendix D.1.

TABLE 5.   Duration of Exposure to Study Medication
           [Number (%) of Patients]
           (Page 2 of 2)

	Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy N = 79
Completed at Least[a]	200 mg/12 mg N = 78	400 mg/12 mg N = 76	600 mg/12 mg N = 82	
1 Dose	78 (100)	76 (100)	82 (100)	79 (100)
4 Weeks	78 (100)	76 (100)	80 (97.6)	79 (100)
8 Weeks	77 (98.7)	74 (97.4)	80 (97.6)	78 (98.7)
12 Weeks	76 (97.4)	72 (94.7)	79 (96.3)	77 (97.5)
24 Weeks	72 (92.3)	63 (82.9)	76 (92.7)	67 (84.8)
36 Weeks	60 (76.9)	59 (77.6)	72 (87.8)	56 (70.9)
52 Weeks	55 (70.5)	55 (72.4)	70 (85.4)	45 (57.0)
Summary of Exposure, Weeks				
Mean (SD)	45 (13)	44 (16)	48 (12)	42 (15)
Median (Min, Max)	52 (4, 60)	52 (1, 60)	52 (0, 56)	52 (3, 60)

a Study weeks defined in Appendix D.1.

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Concurrent Medications and Prior Antidiabetic Medications

The majority of patients (95%-99%) were taking one or more concurrent medications. The most common concurrent medications across treatments were cardiovascular agents, musculoskeletal agents (analgesics), and anti-infectives. These types of medications were not expected to impact study results.

All patients had been receiving an antidiabetic medication prior to the study as required by the protocol. The majority had been receiving the sulfonylureas glyburide (68%-77%) or glipizide (22%-29%).

Patient Disposition

Three hundred eighteen patients (58%) completed the study as determined by the investigator (Table 6). Completion rates were highest for patients treated with combination therapy (71%-85%) and lowest for patients treated with troglitazone monotherapy (28%-44%); patients treated with glyburide monotherapy had a completion rate of 58%.

The most common reason for withdrawal was lack of efficacy, which ranged from a high of 55% for patients treated with 200 mg troglitazone to a low of 4% for patients treated with 600 mg troglitazone/12 mg glyburide combination therapy. Twenty-five percent of patients treated with glyburide monotherapy withdrew due to lack of efficacy. Withdrawal rates due to adverse events were comparable across all treatment groups.

TABLE 6. Patient Disposition
[Number (%) of Patients]
(Page 1 of 2)

	Troglitazone Monotherapy		
	200 mg	400 mg	600 mg
Randomized to Treatment	78	81	78
Withdrawn Prior to End of Treatment			
Lack of Efficacy	43 (55.1)	32 (39.5)	34 (43.6)
Adverse Event	6 (7.7)	7 (8.6)	6 (7.7)
Lack of Compliance	3 (3.8)	2 (2.5)	3 (3.8)
Pregnancy	0 (0.0)	1 (1.2)	0 (0.0)
Other	4 (5.1)	3 (3.7)	1 (1.3)
Total	56 (71.8)	45 (55.6)	44 (56.4)
Completed study[a]	22 (28.2)	36 (44.4)	34 (43.6)

[a] Based on investigator's response on termination case report form

TABLE 6. Patient Disposition
[Number (%) of Patients]
(Page 2 of 2)

	Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy	Total
	200 mg/ 12 mg	400 mg/ 12 mg	600 mg/ 12 mg		
Randomized to Treatment	78	76	82	79	552
Withdrawn Prior to End of Treatment					
Lack of Efficacy	11 (14.1)	7 (9.2)	3 (3.7)	20 (25.3)	150 (27.2)
Adverse Event	5 (6.4)	8 (10.5)	5 (6.1)	6 (7.6)	43 (7.8)
Lack of Compliance	0 (0.0)	1 (1.3)	2 (2.4)	1 (1.3)	12 (2.2)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other	6 (7.7)	6 (7.9)	2 (2.4)	6 (7.6)	28 (5.1)
Total	22 (28.2)	22 (28.9)	12 (14.6)	33 (41.8)	234 (42.4)
Completed study[a]	56 (71.8)	54 (71.1)	70 (85.4)	46 (58.2)	318 (57.6)

[a] Based on investigator's response on termination case report form

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Patients Included in Efficacy Analyses

The number of patients included in the primary efficacy analyses is summarized in Table 7.

5   **RESULTS**

Efficacy

Primary Efficacy Parameters: FSG and HbA$_{1c}$

10

ITT Population Analyses

Mean changes from baseline in FSG and HbA$_{1c}$ at Week 52 are presented in Table 8. Patients treated with 200 mg/12 mg to 600 mg/12 mg troglitazone/
15   glyburide combination therapy had adjusted mean changes from baseline in FSG of -31.0, -38.0, and -56.4 mg/dL, respectively; these represent mean differences from glyburide of -53.7, -60.8, and -79.1 mg/dL, respectively (all p <0.0001). Patients treated with
20   400 and 600 mg troglitazone monotherapy showed decreases in FSG compared with glyburide; however, these decreases were not significant.

A similar pattern was observed for HbA$_{1c}$. Patients treated with 200 mg/12 mg to 600 mg/12 mg
25   combination therapy had mean changes from baseline of -0.70%, -0.91%, and -1.75%, respectively; these represent mean differences from glyburide in HbA$_{1c}$ of -1.60%, -1.81%, and -2.65%, respectively (all p <0.0001).

30   Patients treated with troglitazone monotherapy had increases from baseline in HbA$_{1c}$. The increase was significantly different from glyburide at the 200-mg dose of troglitazone (1.92% compared with 0.90% for glyburide). This may have been attributed to carrying
35   forward data from the patients treated with 200 mg

TABLE 7. Patients Included in Primary Efficacy Analyses[a] at Week 52 (Number of Patients)

	Troglitazone Monotherapy			Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy
	200 mg	400 mg	600 mg	200 mg/ 12 mg	400 mg/ 12 mg	600 mg/ 12 mg	
Randomized	78	81	78	78	76	82	79
No. of Patients in ITT Analysis	78	78	76	78	76	80	79
Total No. of Patients in the Completer Analysis	22	37	34	55	55	70	45

a For FSG

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troglitazone that withdrew from the study due to lack
of efficacy; 55% of patients in this treatment group
withdrew due to lack of efficacy.

The decrease from baseline in FSG at the
5   600-mg/12-mg dose of combination therapy was
significantly greater than the decrease at the
200-mg/12-mg dose of combination therapy compared with
glyburide (p = 0.009). Treatment effects were
consistent across centers for the primary parameters.

10   The mean changes from baseline in FSG and HbA_{1c} at
Week 52 are illustrated in Figure 3.

TABLE 8. Change From Baseline at Month 12 in Primary Glycemic Parameters
ITT Population: Study 991-055
(Page 1 of 2)

Parameter	Troglitazone Monotherapy		
	200 mg	400 mg	600 mg
Fasting Serum Glucose, mg/dL			
N	78	78	76
Mean Baseline	226.3	212.9	230.2
Adjusted Mean Change From Baseline (SE)	42.4 (7.0)	20.6 (7.0)	11.1 (7.1)
Adjusted Mean Difference From Glyburide Monotherapy (SE)[a]	19.6 (9.7)	-2.2 (9.7)	-11.6 (9.7)
95% Confidence Interval[b]	(-5.3, 44.6)	(-27.1, 22.8)	(-36.7, 13.4)
Hemoglobin A_{1c}, %			
N	78	79	76
Mean Baseline	9.54	9.44	9.71
Adjusted Mean Change From Baseline (SE)	1.92 (0.20)	0.85 (0.20)	0.93 (0.20)
Adjusted Mean Difference From Glyburide Monotherapy (SE)[a]	1.02* (0.28)	-0.05 (0.28)	0.03 (0.28)
95% Confidence Interval[b]	(0.31, 1.74)	(-0.76, 0.66)	(-0.69, 0.75)

[a] ANCOVA with treatment and center effects and baseline as covariate using stepdown test of linear-trend or Bonferroni-Holm adjustment.
[b] 95% confidence intervals based on Dunnett's test.
* $p \leq 0.001$
** $p \leq 0.0001$

TABLE 8. Change From Baseline at Month 12 in Primary Glycemic Parameters ITT Population: Study 991-055
(Page 2 of 2)

Parameter	Combination Therapy:Troglitazone/Glyburide			Glyburide Monotherapy
	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
Fasting Serum Glucose, mg/dL				
N	78	76	80	79
Mean Baseline	225.7	230.9	220.8	222.2
Adjusted Mean Change From Baseline (SE)	-31.0 (7.0)	-38.0 (7.1)	-56.4 (6.9)	22.7 (6.9)
Adjusted Mean Difference From Glyburide Monotherapy (SE)[a]	-53.7** (9.7)	-60.8** (9.7)	-79.1** (9.6)	
95% Confidence Interval[b]	(-78.6, -28.9)	(-85.8, -35.7)	(-103.9, -54.4)	
Hemoglobin A$_{1c}$, %				
N	78	76	80	79
Mean Baseline	9.49	9.72	9.45	9.57
Adjusted Mean Change From Baseline (SE)	-0.70 (0.20)	-0.91 (0.20)	-1.75 (0.20)	0.90 (0.20)
Adjusted Mean Difference From Glyburide Monotherapy (SE)[a]	-1.60** (0.28)	-1.81** (0.28)	-2.65** (0.28)	--
95% Confidence Interval[b]	(-2.31, -0.88)	(-2.53, -1.10)	(-3.36, -1.94)	

[a] ANCOVA with treatment and center effects and baseline as covariate using stepdown test of linear-trend or Bonferroni-Holm adjustment.
[b] 95% confidence intervals based on Dunnett's test.
*   p ≤0.001
** p ≤0.0001

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Figure 4 illustrates the mean levels of FSG and HbA$_{1c}$ over time for the ITT population. The majority of improvement in glycemic control (FSG) was observed by the fourth week of therapy.

5

Completers Analyses

Results of the analysis of the completer population were similar to the results for the ITT population for patients treated with combination

10   therapy (Table 9); patients (completers) treated with all doses of combination therapy had significant reductions (p <0.0001) in FSG and HbA$_{1c}$ compared with glyburide. However, HbA$_{1c}$ decreased significantly (p $\leq$0.05) compared with glyburide monotherapy for

15   patients treated with 400 and 600 mg troglitazone monotherapy; this finding is applicable only to the 44% of patients completing the 1-year study.

TABLE 9. Primary Parameters at Week 52: Completers
(Page 1 of 2)

Parameter	Troglitazone Monotherapy		
	200 mg	400 mg	600 mg
Hemoglobin A_{1c}, %			
N	21	37	34
Mean Baseline (SD)	9.53 (1.57)	9.07 (1.61)	9.35 (1.77)
Adjusted Mean Change From Baseline (SE)	0.55 (0.38)	-0.25 (0.29)	-0.26 (0.30)
Adjusted Mean Difference From Glyburide Monotherapy (SE)	-0.23 (0.46)	-1.03* (0.38)	-1.04* (0.39)
95% Confidence Interval[a]	(-1.43 to 0.97)	(-2.02 to -0.04)	(-2.06 to -0.02)
Fasting Serum Glucose, mg/dL			
N	22	37	34
Mean Baseline (SD)	217.5 (44.6)	196.8 (42.4)	212.4 (48.9)
Adjusted Mean Change From Baseline (SE)	13.4 (12.0)	-20.5 (9.4)	-11.7 (9.8)
Adjusted Mean Difference From Glyburide Monotherapy (SE)	0.3 (14.6)	-33.6* (12.3)	-24.8 (12.6)
95% Confidence Interval[a]	(-37.6, 38.2)	(-65.5, -1.8)	(-57.5, 7.8)

[a] ANCOVA (with treatment and center effects and baseline as covariate).
* $p \leq 0.05$
** $p \leq 0.0001$

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TABLE 9. Primary Parameters at Week 52: Completers
(Page 2 of 2)

Parameter	Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy
	200 mg/ 12 mg	400 mg/ 12 mg	600 mg/ 12 mg	
Hemoglobin A_{1c}, %				
N	55	55	70	45
Mean Baseline (SD)	9.33 (1.35)	9.60 (1.32)	9.35 (1.53)	9.49 (1.33)
Adjusted Mean Change From Baseline (SE)	-0.85 (0.24)	-1.10 (0.24)	-1.96 (0.21)	0.78 (0.27)
Adjusted Mean Difference From Glyburide Monotherapy (SE).	-1.63** (0.35)	-1.88** (0.34)	-2.74** (0.33)	--
95% Confidence Interval[a]	(-2.54 to -0.73)	(-2.77 to -0.99)	(-3.60 to -1.88)	
Fasting Serum Glucose, mg/dL				
N	55	55	70	45
Mean Baseline (SD)	221.7 (55.7)	224.6 (43.0)	218.5 (51.1)	214.7 (34.5)
Adjusted Mean Change From Baseline (SE)	-34.1 (7.6)	-46.0 (7.7)	-58.1 (6.8)	13.1 (8.6)
Adjusted Mean Difference From Glyburide Monotherapy (SE)	-47.2** (11.2)	-59.1** (11.1)	-71.2** (10.6)	--
95% Confidence Interval[a]	(-76.3, -18.1)	(-87.8, -30.4)	(-98.7, -43.7)	

[a] ANCOVA (with treatment and center effects and baseline as covariate).
* p ≤0.05
** p ≤0.0001

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Secondary Efficacy Parameters: ITT Population

Total Insulin and C-Peptide

   In general, patients treated with troglitazone

5   mono- and combination therapy showed a significant
(p ≤0.05) decrease in total insulin compared with
glyburide at Week 52 (Table 10).

   Significant (p ≤0.05) decreases in C-peptide were
observed for troglitazone monotherapy only (200 and

10   600 mg troglitazone).   It is unclear to what extent
these decreases observed are due to the withdrawal of
the insulin stimulatory effect associated with
sulfonylurea therapy or to a true drug effect (increase
in insulin sensitivity).   However, decreases in total

15   insulin for combination therapy likely represent a true
drug effect (since the insulin stimulatory effect of
the sulfonylurea is not removed) and indicate an
improvement in insulin sensitivity.

   For patients who completed the study (completers),

20   patients treated with 400 and 600 mg troglitazone had
decreases in total insulin that were significantly
different from glyburide (p <0.05).   There were no
significant differences in C-peptide from glyburide for
any dose of mono- or combination therapy.

TABLE 10.   Total Insulin and C-Peptide at Week 52:   ITT
(Page 1 of 2)

Parameter	Troglitazone Monotherapy		
	200 mg N = 78	400 mg N =78	600 mg N = 76
Total Insulin, μIU/mL			
Mean Baseline (SD)	32.3 (30.6)	33.0 (18.4)	30.5 (17.7)
Adjusted Mean Change From Baseline (SE)	-8.41 (1.39)	-5.90 (1.40)	-11.53 (1.42)
Adjusted Mean Difference From Glyburide	-6.96*	-4.44*	-10.07*
(95% Confidence Interval)	(-11.96 to -1.96)	(-9.45 to 0.59)	(-15.09 to -5.06)
C-Peptide, ng/mL			
Mean Baseline (SD)	2.9 (1.1)	3.1 (1.2)	3.0 (1.2)
Adjusted Mean Change From Baseline (SE)	-0.96 (0.07)	-0.78 (0.07)	-1.01 (0.08)
Adjusted Mean Difference From Glyburide	-0.29*	-0.11	-0.34*
(95% Confidence Interval)	(-0.56, -0.02)	(-0.38, 0.16)	(-0.61, -0.07)

* p ≤0.05

TABLE 10. Total Insulin and C-Peptide at Week 52: ITT
(Page 2 of 2)

Parameter	Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy N = 79
	200 mg/12 mg N = 78	400 mg/12 mg N = 76	600 mg/12 mg N = 80	
Total Insulin, μIU/mL				
Mean Baseline (SD)	28.2 (13.3)	24.9 (10.6)	26.4 (13.9)	27.3 (14.2)
Adjusted Mean Change From Baseline (SE)	-3.84 (1.39)	-5.88 (1.42)	-6.08 (1.38)	-1.45 (1.39)
Adjusted Mean Difference From Glyburide	-2.39	-4.43*	-4.63*	--
(95% Confidence Interval)	(-7.37 to 2.59)	(-9.45 to 0.58)	(-9.58 to 0.32)	--
C-Peptide, ng/mL				
Mean Baseline (SD)	2.8 (1.1)	2.6 (0.9)	2.9 (1.1)	2.7 (0.9)
Adjusted Mean Change From Baseline (SE)	-0.75 (0.07)	-0.76 (0.08)	-0.76 (0.07)	-0.67 (0.07)
Adjusted Mean Difference From Glyburide	-0.08	-0.09	-0.09	--
(95% Confidence Interval)	(-0.35, 0.18)	(-0.35, 0.18)	(-0.36, 0.17)	--

* P ≤0.05

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HbA_{1c} and Glucose Responders

Table 11 indicates the number of patients who had a ≥ 30 mg/dL reduction in FSG or a $\geq 1\%$ reduction in HbA$_{1C}$ (responders) at Week 52. Patients treated with all doses of combination therapy had a significantly higher (p ≤ 0.001) responder rate for HbA$_{1C}$ and FSG compared with glyburide. Sixty-six percent and 64% of patients treated with 600 mg/12 mg combination therapy met the responder criteria for FSG and HbA$_{1C}$, respectively.

TABLE 11. Responders at Week 52: ITT
(Page 1 of 2)

Responders as Defined by:	Troglitazone Monotherapy (mg)		
	200 N = 78	400 N = 78	600 N = 76
≥30 mg/dL Reduction in FSG[a]			
Responders, N (%)	11 (14)	20 (26)	18 (24)
≥1% Reduction in HbA$_{1c}$[a]			
Responders, N (%)	3 (4)	13 (17)	8 (11)

* p ≤0.001, significantly different from glyburide (based on step-down CMH tests)
a From baseline

TABLE 11. Responders at Week 52: ITT
(Page 2 of 2)

Responders as Defined by:	Troglitazone/Glyburide (mg) Combination Therapy			Glyburide
	200/12 N = 78	400/12 N = 76	600/12 N = 80	
≥30 mg/dL Reduction in FSG[a]				
Responders, N (%)	37* (47)	47* (62)	53* (66)	10 (13)
≥1% Reduction in HbA$_{1C}$[a]				
Responders, N (%)	29* (37)	39* (51)	51* (64)	4 (5)

* p ≤0.001, significantly different from glyburide (based on step-down CMH tests)

a From baseline

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These improvements in glycemic control are further
illustrated by the number of patients who had an HbA_{1c}
of $\leq 8\%$ (Figure 5). Thirty-three percent, 33%, and 60%
of patients treated with 200 mg/12 mg to 600 mg/12 mg

5   combination therapy, respectively, had an HbA_{1c} of $\leq 8\%$
at the end of the study compared with 10% of glyburide-
treated patients. In addition, 22%, 21%, and 41% of
patients treated with 200 mg/12 mg to 600 mg/12 mg
combination therapy, respectively, had an HbA_{1c} of $\leq 7\%$

10   at Week 52 compared with 1% of patients treated with
glyburide monotherapy.

Lipid Parameters

       Fasting serum lipid profiles were determined at

15   baseline and periodically through Week 52. Apo A1,
Apo B, and Lp(a) were determined only at baseline,
Month 6, and Month 12 as part of a special laboratory
panel. Summary statistics for lipid parameters are
shown in Table 12.

20   Mean triglyceride levels decreased for all
therapies with the exception of glyburide, which showed
a mean increase at Month 12. Mean decreases were
clinically significant for combination therapy, which
ranged from -33 to -51 mg/dL (difference from

25   glyburide, -47 to -65 mg/dL), in contrast with
glyburide monotherapy, which showed a mean increase in
triglycerides of 14 mg/dL.
       Mean levels of HDL increased for patients treated
with both mono- and combination therapy

30   (0.9-4.5 mg/dL), with the exception of the 400 mg/12 mg
combination therapy, which showed a slight decrease.
The adjusted mean change from baseline in HDL was
significantly greater (p <0.05) than glyburide for
patients treated with 600 mg troglitazone monotherapy

35   (difference from glyburide, 4.9 mg/dL).

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Mean levels of total cholesterol increased at
Month 12 across all treatment groups. Adjusted mean
increases were significantly (p <0.05) different from
glyburide for all doses of troglitazone (differences
5   from glyburide: 25, 26, and 28 mg/dL for 200, 400, and
600 mg, respectively). Mean LDL also increased across
all treatment groups; adjusted mean increases were
significantly different (p <0.05) from glyburide for
patients treated with 200 mg and 600 mg troglitazone
10   (difference from glyburide: 23 and 19 mg/dL,
respectively). There were no clinically or
statistically significant changes in VLDL.

There were no statistically significant changes in
free fatty acids, Apo A, or Apo B. Lp(a) increased
15   across all treatment groups; the increases in adjusted
means were significantly (p <0.05) different from
glyburide for patients treated with 400 and 600 mg mono
and combination therapy. These increases are not
thought to be clinically significant.

20   Overall, the changes in lipid profiles indicate
that troglitazone, either as monotherapy or combination
therapy, do not negatively impact atherogenic risk in
patients with NIDDM and instead may show a potential
clinical benefit.

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TABLE 12a. Lipid Parameters at Week 52: ITT Population
(Page 1 of 2)

Parameter	Troglitazone Monotherapy		
	200 mg	400 mg	600 mg
Total Cholesterol, mg/dL			
N	78	77	76
Baseline			
Mean	227.97	215.77	217.45
(SD)	(65.04)	(43.03)	(44.50)
Median	216.50	208.00	210.00
(Min, Max)	(150.0, 663.0)	(120.0, 337.0)	(140.0, 346.0)
Change From Baseline			
Mean	19.96	24.78	25.88
(SD)	(58.37)	(45.32)	(46.64)
Median	21.00	20.00	20.50
(Min, Max)	(-347, 126.0)	(-94.0, 165.0)	(-113, 192.0)
LDL Cholesterol, mg/dL			
N	78	77	76
Baseline			
Mean	137.33	129.32	131.43
(SD)	(39.07)	(31.42)	(38.20)
Median	132.00	129.00	130.50
(Min, Max)	(65.0, 243.0)	(47.0, 221.0)	(50.0, 240.0)
Change From Baseline			
Mean	17.78	12.09	16.21
(SD)	(41.17)	(31.49)	(34.29)
Median	20.50	11.00	15.00
(Min, Max)	(-149, 132.0)	(-95.0, 89.0)	(-71.0, 88.0)

TABLE 12a. Lipid Parameters at Week 52: ITT Population
(Page 2 of 2)

Parameter	Combination Therapy:Troglitazone/Glyburide			Glynase
	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
Total Cholesterol, mg/dL				
N	78	76	79	78
Baseline				
Mean	208.97	218.00	212.71	215.50
(SD)		(45.15)	(41.71)	(39.94)
Median	205.50	218.50	209.00	209.00
(Min, Max)	(106.0, 380.0)	(133.0, 305.0)	(134.0, 356.0)	(131.0, 326.0)
Change From Baseline				
Mean	15.55	7.71	11.58	6.17
(SD)	(34.34)	(39.09)	(42.95)	(36.74)
Median	17.00	13.50	4.00	6.50
(Min, Max)	(-73.0, 96.0)	(-85.0, 161.0)	(-91.0, 140.0)	(-113, 122.0)
LDL Cholesterol, mg/dL				
N	78	76	79	78
Baseline				
Mean	117.53	126.87	121.80	132.27
(SD)	(37.84)	(30.75)	(33.16)	(31.51)
Median	117.00	126.50	119.0	131.00
(Min, Max)	(3.0, 240.0)	(49.0, 217.0)	(54.0, 215.0)	(70.0, 212.0)
Change From Baseline				
Mean	14.74	8.63	12.70	3.49
(SD)	(36.33)	(31.75)	(33.39)	(27.83)
Median	13.50	8.50	14.00	4.00
(Min, Max)	(-69.0, 130.0)	(-66.0, 131.0)	(-66.0, 121.0)	(-60.0, 84.0)

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TABLE 12b. Lipid Parameters at Week 52: ITT Population
(Page 1 of 2)

Parameter	Troglitazone Monotherapy			
	200 mg	400 mg	600 mg	
VLDL Cholesterol, mg/dL				
N	78	77	76	
Baseline				
Mean	48.49	44.27	54.67	
(SD)	(31.05)	(26.94)	(40.67)	
Median	42.50	39.00	44.00	
(Min, Max)	(8.0, 170.0)	(3.0, 152.0)	(16.0, 243.0)	
Change From Baseline				
Mean	3.54	8.48	-0.36	
(SD)	(26.20)	(34.65)	(46.41)	
Median	3.50	3.00	-3.00	
(Min, Max)	(-8.10, 104.0)	(-47.0, 168.0)	(-145, 223.0)	
HDL Cholesterol, mg/dL				
N	78	77	76	
Baseline				
Mean	36.87	37.73	37.68	
(SD)	(8.97)	(16.24)	(17.75)	
Median	35.50	36.00	35.00	
(Min, Max)	(21.0, 70.0)	(14.0, 144.0)	(16.0, 158.0)	
Change From Baseline				
Mean	0.86	2.99	4.53	
(SD)	(6.72)	(14.98)	(24.83)	
Median	1.00	3.00	3.00	
(Min, Max)	(-18.0, 19.0)	(-94.0, 66.0)	(-112, 160.0)	

TABLE 12b.　Lipid Parameters at Week 52:　ITT Population
(Page 2 of 2)

Parameter	Combination Therapy:Troglitazone/Glyburide			Glyburide Monotherapy
	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
VLDL Cholesterol, mg/dL				
N	78	76	79	78
Baseline				
Mean	51.06	54.51	51.42	46.81
(SD)	(41.61)	(34.10)	(37.56)	(33.35)
Median	41.50	46.00	39.00	38.00
(Min, Max)	(5.0, 285.0)	(7.0, 191.0)	(3.0, 239.0)	(9.0, 197.0)
Change From Baseline				
Mean	3.36	-4.47	-4.01	-2.78
(SD)	(23.93)	(30.71)	(29.14)	(27.77)
Median	2.00	-3.00	-3.00	-1.00
(Min, Max)	(-96.0, 58.0)	(-138, 90.0)	(-80.0, 69.0)	(-133, 127.0)
HDL Cholesterol, mg/dL				
N	78	76	79	78
Baseline				
Mean	36.63	38.34	35.01	35.71
(SD)	(11.63)	(18.74)	(11.60)	(7.37)
Median	34.50	35.00	33.00	35.00
(Min, Max)	(17.0, 100.0)	(22.0, 146.0)	(18.0, 110.0)	(18.0, 58.0)
Change From Baseline				
Mean	1.67	-1.76	4.47	-0.15
(SD)	(14.35)	(18.99)	(15.75)	(5.97)
Median	1.00	-0.50	3.00	-1.00
(Min, Max)	(-70.0, 90.0)	(-122, 17.0)	(-82.0, 81.0)	(-13.0, 20.0)

TABLE 12c. Lipid Parameters at Week 52: ITT Population
(Page 1 of 2)

	Troglitazone Monotherapy		
	200 mg	400 mg	600 mg
Triglycerides, mg/dL			
N	78	77	76
Baseline			
Mean	275.54	273.21	279.76
(SD)	(459.17)	(327.86)	(239.93)
Median	201.50	198.00	212.00
(Min, Max)	(74.0, 4120)	(47.0, 2770)	(83.0, 1741)
Change From Baseline			
Mean	-35.77	-3.86	-9.59
(SD)	(414.77)	(333.10)	(307.28)
Median	3.50	-2.00	-24.00
(Min, Max)	(-3514, 365.0)	(-2281, 1062)	(-1027, 2186)
Free Fatty Acids, mEq/L			
N	78	78	76
Baseline			
Mean	0.74	0.86	0.81
(SD)	(0.33)	(0.50)	(0.84)
Median	0.68	0.78	0.73
(Min, Max)	(0.1, 2.3)	(0.3, 3.6)	(0.3, 7.7)
Change From Baseline			
Mean	-0.09	-0.17	-0.19
(SD)	(0.33)	(0.54)	(0.89)
Median	-0.04	-0.12	-0.11
(Min, Max)	(-1.7, 0.6)	(-3.0, 0.8)	(-7.4, 1.1)

TABLE 12c. Lipid Parameters at Week 52: ITT Population
(Page 2 of 2)

| Parameter | Combination Therapy:Troglitazone/Glyburide | | | Glyburide Monotherapy |
	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
Triglycerides, mg/dL				
N	78	76	79	78
Baseline				
Mean	284.19	265.78	251.71	223.40
(SD)	(383.59)	(185.17)	(205.06)	(156.11)
Median	194.50	218.00	198.00	176.50
(Min, Max)	(55.0, 3215)	(56.0, 1129)	(39.0, 1594)	(53.0, 831.0)
Change From Baseline				
Mean	-32.86	-37.33	-50.46	14.24
(SD)	(248.21)	(149.09)	(177.90)	(145.74)
Median	-3.00	-15.00	-39.00	8.00
(Min, Max)	(-1795, 487.0)	(-890, 388.0)	(-1091, 618.0)	(-467, 831.0)
Free Fatty Acids, mEq/L				
N	78	76	80	79
Baseline				
Mean	0.72	0.79	0.70	0.76
(SD)	(0.38)	(0.40)	(0.23)	(0.49)
Median	0.66	0.72	0.66	0.68
(Min, Max)	(0.3, 2.7)	(0.3, 3.0)	(0.2, 1.4)	(0.3, 3.8)
Change From Baseline				
Mean	-0.12	-0.15	-0.08	-0.05
(SD)	(0.36)	(0.37)	(0.26)	(0.51)
Median	-0.10	-0.12	-0.09	0.03
(Min, Max)	(-1.3, 0.8)	(-2.2, 0.9)	(-0.5, 0.6)	(-3.5, 0.9)

TABLE 12d. Lipid Parameters at Week 52: ITT Population
(Page 1 of 2)

Parameter	Troglitazone Monotherapy		
	200 mg	400 mg	600 mg
Apo A1[a], mg/dL			
N	22	37	35
Baseline			
Mean	143.9	138.6	138.3
(SD)	(20.4)	(23.6)	(24.8)
Median			
(Min, Max)	(108, 190)	(103.5, 203.0)	(94.5, 197.0)
Change From Baseline			
Mean	1.9	-1.5	-1.9
(SD)	(14.2)	(15.4)	(21.1)
Median			
(Min, Max)	(-21.5, 26.5)	(-53.0, 40.0)	(-54.5, 57.5)
Apo B[a], mg/dL			
N	22	37	35
Baseline			
Mean	134.9	124.2	118.2
(SD)	(31.8)	(28.4)	(30.0)
Median			
(Min, Max)	(94.0, 209.5)	(77.5, 198.5)	(68.0, 199.5)
Change From Baseline			
Mean	6.4	3.4	3.1
(SD)	(29.0)	(35.5)	(37.9)
Median			
(Min, Max)	(-55.0, 59.5)	(-99.0, 121.5)	(-60.5, 172.0)

TABLE 12d. Lipid Parameters at Week 52: ITT Population
(Page 2 of 2)

Parameter	Combination Therapy:Troglitazone/Glyburide			Glyburide Monotherapy
	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
Apo A1[a], mg/dL				
N	56	56	70	47
Baseline				
Mean	142.4	140.1	138.1	141.5
(SD)	(23.7)	(21.4)	(22.3)	(20.8)
Median				
(Min, Max)	(90.0, 211.0)	(83.5, 198.0)	(93.5, 212.0)	(108, 208)
Change From Baseline				
Mean	-1.2	-4.8	-4.9	-1.1
(SD)	(18.5)	(20.7)	(14.1)	(14.2)
Median				
(Min, Max)	(-44.0, 67.5)	(-60.0, 89.0)	(-33.5, 38.0)	(-53.5, 38.0)
Apo B[a], mg/dL				
N	56	56	70	47
Baseline				
Mean	117.4	123.5	117.6	124.5
(SD)	(26.7)	(25.3)	(23.7)	(21.5)
Median				
(Min, Max)	(68.0, 211.0)	(80.5, 181.5)	(67.0, 190.5)	(85.0, 166.0)
Change From Baseline				
Mean	6.3	0.1	-0.7	2.9
(SD)	(20.4)	(23.3)	(21.7)	(23.0)
Median				
(Min, Max)	(-42.5, 85.5)	(-66.0, 58.0)	(-55.5, 66.0)	(-52.5, 101.5)

TABLE 12e. Lipid Parameters at Week 52: ITT Population
(Page 1 of 2)

Parameter	Troglitazone Monotherapy		
	200 mg	400 mg	600 mg
Lp(a)[a], mg/dL			
N	22	37	35
Baseline			
Mean	23.4	24.1	14.3
(SD)	(21.7)	(24.9)	(19.4)
Median			
(Min, Max)	(0.8, 82.5)	(0.8, 76.5)	(0.8, 84.0)
Change From Baseline			
Mean	8.8	10.0	9.1
(SD)	(13.2)	(12.0)	(11.7)
Median			
(Min, Max)	(-10.0, 38.0)	(-9.5, 33.5)	(-8.0, 36.5)

TABLE 12e.   Mean Lipid Parameters at Week 52:   ITT Population
(Page 2 of 2)

| Parameter | Combination Therapy:Troglitazone/Glyburide | | | Glyburide Monotherapy |
	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
Lp(a)[a], mg/dL				
N	56	56	70	47
Baseline				
Mean	25.4	22.4	16.8	16.5
(SD)	(29.0)	(27.5)	(23.0)	(19.9)
Median				
(Min, Max)	(0.8, 131.0)	(0.8, 131.0)	(0.8, 134.5)	(0.8, 94.5)
Change From Baseline				
Mean	7.0	10.7	10.4	1.4
(SD)	(12.5)	(18.0)	(18.1)	(11.3)
Median				
(Min, Max)	(-28.5, 46.5)	(-5.0, 75.5)	(-33.0, 95.1)	(-13.0, 68.5)

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Blood Pressure

    In general, patients included in this study were
not hypertensive; the mean blood pressure (BP) for the
study population was approximately 129/78 mm Hg.

5   Patients treated with 600 mg/12 mg combination therapy
had a significant decrease in mean diastolic BP
($p < 0.05$) compared with glyburide monotherapy (decrease
of -2.6 mm Hg compared to glyburide).

10   Meal Tolerance Testing

    Meal tolerance testing was performed in a subset
of patients at baseline and at Months 6 and 12.
Postprandial glucose, insulin, and C-peptide levels
were determined at 30, 60, 90, and 120 minutes after a

15   standard meal (Sustacal HC) (Table 13).

    At Month 12, the mean glucose AUC(0-2 hr)
decreased significantly ($p \leq 0.05$) compared with
glyburide for patients treated with all dose levels of
troglitazone/glyburide combination therapy and 600 mg

20   troglitazone monotherapy. All doses of monotherapy and
combination therapy showed decreases in insulin and
C-peptide AUC(0-2 hr); however, none of these decreases
reached statistical significance.

TABLE 13.　Mean Change From Baseline[a] in AUC (0-2 hrs) 2 Hours After Standard Meal at Month 12: Completers
(Page 1 of 2)

Parameter	Troglitazone Monotherapy		
	200 mg N = 8	400 mg N = 8	600 mg N = 11
Glucose AUC (0-2 hr), mg/dL-hr			
Baseline (SD)	574 (104)	568 (103)	558 (97)
Change From Baseline at Month 12 (SD)	5 (97)	37 (170)	-137* (123)
Total Insulin AUC (0-2 hr), μIU/mL-hr			
Baseline (SD)	154.6 (110.0)	140.8 (69.0)	171.0 (72.3)
Change From Baseline at Month 12 (SD)	-46.7 (27.1)	-54.1 (55.3)	-65.5 (44.6)
C-Peptide AUC (0-2 hr), ng/mL-hr			
Baseline (SD)	8.3 (3.9)	9.7 (3.4)	10.4 (3.7)
Change From Baseline at Month 12 (SD)	-2.2 (1.9)	-4.2 (2.7)	-3.1 (3.0)

[a] Negative change from baseline indicates improvement
* $p \leq 0.05$, based on ANCOVA including effects for center, treatment, and baseline as a covariate. Adjusted mean changes are presented in Appendix D.5.

TABLE 13. Mean Change From Baseline[a] in AUC (0-2 hrs) 2 Hours After
Standard Meal at Month 12: Completers
(Page 2 of 2)

Parameter	Combination Therapy:Troglitazone/Glyburide			Glyburide Monotherapy N = 12
	200 mg/12 mg N = 13	400 mg/12 mg N = 13	600 mg/12 mg N = 15	
Glucose AUC (0-2 hr), mg/dL·hr				
Baseline (SD)	629 (156)	598 (72)	583 (110)	582 (77)
Change From Baseline at Month 12 (SD)	-155* (183)	-114* (103)	-94* (138)	35 (88)
Total Insulin AUC (0-2 hr), μIU/mL·hr				
Baseline (SD)	148.9 (66.5)	123.2 (51.4)	133.7 (75.1)	124.2 (45.3)
Change From Baseline at Month 12 (SD)	-39.7 (40.1)	-25.1 (37.3)	-27.1 (56.6)	-21.7 (28.6)
C-Peptide AUC (0-2 hr), ng/mL·hr				
Baseline (SD)	10.0 (4.5)	9.8 (5.2)	10.1 (2.9)	8.8 (2.7)
Change From Baseline at Month 12 (SD)	-3.7 (3.0)	-3.8 (3.4)	-2.9 (2.4)	-2.3 (2.6)

[a] Negative change from baseline indicates improvement
* $p \leq 0.05$, based on ANCOVA including effects for center, treatment, and baseline as a covariate. Adjusted mean changes are presented in Appendix D.5.

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Weight

Statistically significant (p ≤0.0001) increases in
mean body weight (6-13 lbs) occurred in patients
treated with all doses of combination therapy compared
5   with glyburide (Table 14); patients treated with
glyburide monotherapy showed a mean weight loss of
1 lb. Patients treated with troglitazone monotherapy
showed mean decreases from baseline of 1 to 7 lbs.
This increase in weight for patients on combination
10   therapy is possibly a result of improved glycemic
control, decreased glycosuria, or a potentiation of the
known effect of sulfonylurea therapy on weight gain.

TABLE 14. Mean Change From Baseline in Body Weight at Month 12: ITT (Page 1 of 2)

	Troglitazone Monotherapy (mg)		
	200 N = 79	400 N = 78	600 N = 76
Mean Baseline (SD)	201.7 (42.0)	216.6 (54.8)	207.1 (46.1)
Adjusted Mean Change (SE)	-6.9 (1.2)	-3.9 (1.2)	-0.8 (1.2)
Difference From Glyburide (SE)	-5.6* (1.6)	-2.6 (1.6)	0.5 (1.6)

* $p \leq 0.05$.
** $p \leq 0.0001$.

5

TABLE 14. Mean Change From Baseline in Body Weight at Month 12: ITT

| | Troglitazone/Glyburide (mg) Combination Therapy | | | Glyburide |
	200/12 N = 77	400/12 N = 75	600/12 N = 79	N = 79
Mean Baseline (SD)	202.5 (35.8)	200.6 (42.4)	196.2 (43.2)	196.2 (43)
Adjusted Mean Change (SE)	5.8 (1.2)	7.7 (1.2)	13.1 (1.2)	-1.3 (1.2)
Difference From Glyburide (SE)	7.1** (1.6)	9.0** (1.6)	14.4** (1.6)	-- --

* $p \leq 0.05$
** $p \leq 0.0001$

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Diabetes Symptoms Assessment

Ten common symptoms of diabetes, including
fatigue, frequent urination, and thirst, were assessed
for severity (0 = absent, 1 = mild, 2 = moderate,
5   3 = severe) at baseline and monthly throughout the
study. Mean baseline scores were generally below one
for all 10 symptoms and mean scores remained below
one at the end of the study.

10   **Pharmacokinetic Analysis: Plasma Trough Concentrations
of Troglitazone**

Individual trough plasma troglitazone
concentrations are shown in Appendix E. Mean trough
plasma concentrations of troglitazone at Week 12 are
15   summarized in Table 15.

TABLE 15. Mean (%RSD) Trough Plasma Concentrations (ng/mL) of Troglitazone at Week 12

Troglitazone 200 mg QD (N=48)	Troglitazone 200 mg QD + Glyburide (N=76)	Troglitazone 400 mg QD (N=54)	Troglitazone 400 mg QD + Glyburide (N=70)	Troglitazone 600 mg QD (N=61)	Troglitazone 600 mg QD + Glyburide (N=77)
145 (150%)	111 (70%)	238 (76%)	181 (70%)	285 (86%)	291 (93%)

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Variability in trough plasma troglitazone
concentrations was high as reflected by the large %RSD
values. Mean trough troglitazone concentrations
generally increased with increasing troglitazone doses.
5   The trough concentrations obtained in this study using
troglitazone tablets from Lots CM 1581194 and
CM 0120295 were similar to those observed in the
corresponding dose groups in a dose-proportionality
study using troglitazone tablets from Lot CM 1581194.
10   For each troglitazone dose group, mean trough plasma
troglitazone concentrations for the troglitazone
monotherapy appeared similar to those for
troglitazone/glyburide combination therapy. This is
consistent with the results of a study indicating a
15   lack of pharmacokinetic interaction between glyburide
and troglitazone.

Safety

20   **Adverse Events**
Adverse events that were treatment emergent (not
present at baseline) are summarized in the following
section using a modified COSTART dictionary. If,
however, an adverse event present at baseline increased
25   in intensity or frequency during treatment, the event
was included in the summaries. Each patient reporting
an adverse event was counted only once for that event
regardless of the number of times the adverse event was
reported. Associated adverse events were those
30   considered by the investigator to be possibly,
probably, or definitely related to study therapy.

Overview
Troglitazone monotherapy and troglitazone/
35   glyburide combination therapy were well-tolerated
throughout the study. Overall, 70% of patients treated

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with troglitazone monotheraphy had adverse events
compared with 90% of patients treated with glyburide
(control) therapy. Patients treated with combination
theraphy had an incidence of adverse events similar to
glyburide therapy, 91%. To what extent the high
dropout rate for troglitazone monotheraphy affected the
incidence of adverse events is not known.

In general, the incidence of adverse events was
not influenced by age or menopausal status. Overall,
patients treated with combination therapy had a higher
incidence of associated adverse events (26%) compared
with those treated with glyburide (10%).

The incidence of serious adverse events was
similar across all treatments; the percent of patients
withdrawn for adverse events was 8% across treatments.

Clinical Laboratory Measurements

Changes From Baseline to Outside Normal Range

Baseline clinical laboratory parameters were
compared with values at the end of the study (last
visit) to identify any abnormal trends. The percent of
patients with increases or decreases in laboratory
values were calculated based on the number of patients
at risk for changes outside of the reference range;
i.e., patients with low or high values at baseline were
not considered at risk for a decrease or increase,
respectively.

No clinically adverse trends were noted in any
laboratory parameter. However, dramatic improvement
(i.e., decreases) in urine glucose for all combination
therapy groups was evident.

Clinically Important Changes

The Guidelines for Evaluation of Clinical
Laboratory Values were used to identify those patients

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that may have had a clinically important change in one
or more laboratory values at any point during the
study. Laboratory results were then reviewed for these
particular patients to determine which patients

5   actually had clinically important changes in a given
laboratory parameter. Minimal changes occurred within
any laboratory parameter across all treatments.

Patients meeting criteria for clinically important
changes are discussed below. A greater number of

10   patients treated with troglitazone combination therapy
than troglitazone monotherapy had laboratory changes
meeting clinically meaningful change criteria. One
patient had significantly elevated ALT and AST which
was considered attributable to study drug by the

15   investigator and which causality cannot be confidently
ruled out: Patient 4, Center 16, experienced
significantly elevated ALT (1155 U/L) and AST (458 U/L)
following 57 days of troglitazone 600 mg combination
therapy and receiving a flu vaccine. ALT and AST

20   returned to baseline levels 49 days after therapy was
withdrawn.

Specific Laboratory Parameters

25   Hematology: Minimal changes occurred with any of the
hematological parameters. Changes that met criteria
for possible clinical importance were increases or
decreases within the normal range or transient changes
that subsequently resolved. Patients meeting

30   clinically important changes in hematology parameters
are noted here. Thirty-four patients had changes in
hemoglobin or hematocrit or both meeting criteria for
clinically meaningful change. Seven patients had
mildly transient decreases which returned to baseline

35   levels while remaining on troglitazone (3 patients;
two on 400 mg, one on 600 mg) or troglitazone

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combination (4 patients; three on 400 mg/12 mg, one on
600 mg/12 mg). Eight patients had slight decreases
within the normal range or were near the lower normal
limit at baseline and dropped below normal limits
during the study, and hemoglobin or hematocrit levels
remained stable throughout the study. Eight patients
had levels below normal reference limits for hemoglobin
or hematocrit at baseline and remained below normal
limits throughout the study, none were withdrawn for
this reason. Fourteen patients had decreases in
hemoglobin and hematocrit secondary to blood loss for
several reasons, e.g., acute bleeding due to automobile
accident, rectal bleeding due to hemorrhoids, donated
blood, bleeding ulcer (2 patients), CABG surgery
(4 patients). Two of these patients were consuming up
to 50 concurrent medications and two additional
patients had severe infections associated temporally
with decreased hemoglobin and hematocrit. After
thorough review of patient laboratory data, no patient
experienced clinically important decreases in any
hematological parameter that can be directly
attributable to troglitazone.

Liver Enzymes: Thirteen patients had clinically
meaningful elevations in ALT, AST, or both. Three of
these patients were terminated due to enzymes
elevations; all were followed and enzymes returned to
either baseline or within normal limits. Four
additional patients had transient elevations which
resolved while remaining on troglitazone or
troglitazone combination. Two patients on troglitazone
600 mg combination, three on troglitazone 300 mg
combination, and one patient on troglitazone 200 mg
monotherapy had mildly elevated (<3 x upper normal
limit) at the end of the study. Three of these
patients were concomitantly using many additional

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medications for concurrent illness which cannot be
ruled out as causal or contributory to their elevated
enzymes.

5   DISCUSSION
        Although glitazones (e.g., troglitazone) enhance
insulin action at the cellular level, they do not
stimulate insulin release, nor do they mimic its
action. The therapeutic benefits of glitazone
10   treatment depends on the availability of adequate
amounts of insulin. The addition of a glitazone to
concurrent sulfonylurea treatment provides a balance of
stimulated release of insulin while ameliorating
insulin resistance. The results obtained in this study
15   provide evidence of significant and synergistic
improvement in glycemic control of patients with very
few remaining therapeutic options.

       Glycemic Parameters
20   The mean change from baseline in FSG for the
600T/12G arm was -56 mg/dL, representing a difference
of -79 mg/dL from the control arm. The improvement in
FSG is confirmed by a mean change from baseline in
HbA_{1c} of -1.75% in the same treatment arm, a difference
25   of -2.65% from the active control arm. Approximately
60% of patients in the 600T/12g arm reached an HbA_{1c}
level $\leq$8%. The magnitude of these changes represent an
impressive improvement in glycemic control without the
use of exogenous insulin. Although the glycemic
30   improvements observed in the 400T/12G and the 200T/12G
arms were less pronounced, these data provide the
rationale for titration based on the level of glycemic
control.
        The results of the troglitazone monotherapy
35   treatment arms, on the other hand, should be
interpreted carefully. Considering the slow acting

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properties of troglitazone, an immediate switch from
sulfonylurea to troglitazone would cause a
deterioration in glycemic control before any
improvement is observed. Moreover, the immediate
5   switch in patients who are already in poor control
would worsen the degree of glucose toxicity and make
adequate glycemic control even harder to achieve. This
situation was observed in the monotherapy arms. Those
patients were switched from the maximum dose of
10   glyburide to troglitazone monotherapy at the time of
randomization. Consequently, glycemic control in the
majority of patients worsened, and patients with
excessive hyperglycemia were withdrawn from the study
for safety purposes. Due to the nature of the ITT
15   analysis with LOCF, the average change in FSG and HbA_{1c}
is reflective of the high glycemic values of patients
who discontinued early. In other words, the higher the
early dropout rate, the worse the end of study results
would appear. This is especially the case in the
20   T200 arm since the dropout rate due to lack of efficacy
reached almost 60%. Therefore, the results of the ITT
analysis in this case are not a good reflection of the
true response of all patients. On the other hand, the
results of the completers analysis represent a bias in
25   favor of troglitazone. The completers analysis would
effectively select the sub-population who are more
likely to respond to study medication. The true
response of these treatment arms is more likely to lie
somewhere between the results of the ITT and completers
30   populations. Nevertheless, the clinical interpretation
of these data indicates that switching patients from
sulfonylurea use, particularly those on high doses, to
troglitazone monotherapy is not an appropriate
therapeutic approach.
35   Troglitazone should be added to current treatment
regimens of a sulfonylurea beginning at 200 mg and

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increasing up to 600 mg as needed to optimize glycemic
control. As patients reach target goals of glycemic
control, the dose of sulfonylurea may be reduced or
even eliminated based on the level of glycemic control.
Hence, in these patients (sulfonylurea failures),
troglitazone as monotherapy is achieved only if
warranted based upon glycemic control parameters.
Faced with the alternative of reducing the dosage of
one of the agents, the pathophysiology of the disease
should be considered. Treating the basic defect of
Type II diabetes, i.e., insulin resistance, should take
precedence over exhausting pancreatic insulin secretion
by sulfonylurea stimulation. Therefore, as glycemic
control improves the sulfonylurea should be considered
for dose reduction or even discontinuation if
indicated. Troglitazone alone can be effective in
naive patients who are not well-controlled on diet and
exercise but have not been managed on oral agents. The
deficit in the insulin secretory capacity of naive
patients is generally relative, and the improvement in
insulin sensitivity may be sufficient to restore
normoglycemia.

Insulin, C-peptide, and Meal Tolerance Test
       The insulin reduction observed in the combination
treatment arms reflects an improvement in insulin
sensitivity since the lower insulin level is associated
with significant decreases in FSG and HbA_{1c} rather than
increases. The direction of the change in the fasting
levels of insulin and serum glucose is mirrored by
similar changes in the AUC of the insulin and serum
glucose during the meal tolerance test for the
combination arms. The improved insulin sensitivity
leads to a reduced demand on pancreatic secretion of
insulin, a desirable outcome given the natural
progression of the disease.

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The magnitude of the reduction in insulin in the
monotherapy arms is greater than that observed in the
various combination arms. While a similar reduction
between the monotherapy and the combination treatment
5   arms would have been expected based upon enhanced
insulin activity, the additional decrease in insulin
levels may be attributed to the removal of
sulfonylurea-stimulated insulin secretion. Finally,
the reduction observed in the control arm (micronized
10   glyburide) may be attributed to gradual degradation of
the pancreatic secretory function or secondary failure
typically observed with sulfonylurea treatment over
time. This change cannot be attributed to improvements
in insulin sensitivity, since FSG levels increased and
15   did not decrease. The observed changes in insulin
levels were confirmed by similar changes in direction
and magnitude in C-peptide levels for all treatment
arms.

20   **Lipid Parameters**

The classical manifestations of insulin resistance
in a diabetic population are elevated triglycerides and
low levels of HDL. Therefore, the reversal of insulin
resistance should be expected to elicit favorable
25   changes in these lipid parameters, as observed in this
study. Although statistical significance was reached
in some (but not all) treatment arms, the general trend
of the changes is consistent with the reversal of
insulin resistance, i.e., a reduction in triglycerides
30   and an increase in HDL. The reduction in insulin
levels and resultant increase in lipoprotein lipase
(LPL) activity could be responsible for the
triglyceride and HDL changes. Modest increases of
minimal clinical significance in total cholesterol and
35   LDL were observed in the monotherapy arms. Similar,
but less pronounced changes were observed in the

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combination arms. It is important to note that LDL
levels were measured directly and not calculated
indirectly from triglycerides and cholesterol levels
using the Freidwald formula. Both LDL and cholesterol
are relatively constant parameters and are not affected
by the fasting state of the patient. Triglycerides,
however, are extremely variable, and affected by the
fasting state of the patient. This variability could
explain the fact that a clinically desirable mean
reduction in excess of 50 mg/dL observed in the
T600/G12 group did not reach statistical significance.
In contrast, the magnitude of change in both
cholesterol and LDL was of little clinical significance
(only 4%-7% in the combination treatment arms) but was
statistically significant.

Lipid changes observed in this study are
consistent with results from prior studies. The
favorable change in triglycerides, HDL, and FFA are
contrasted by minimal increases in total cholesterol,
LDL, Lp(a), and no changes in Apo (A1) and Apo (B).
Collectively, these changes may be interpreted as
having a potentially beneficial impact on atherogenic
risk. It should be noted that patients with elevated
triglycerides levels could potentially benefit from
troglitazone treatment and provide synergism to the
management of their dyslipidemia since elevated
triglyceride levels are recognized as an independent
risk factor for cardiovascular disease.

Blood Pressure

No statistically or clinically significant changes
were observed in systolic blood pressure at the end of
the study. Mean diastolic blood pressure, however,
decreased significantly (p <0.05) for patients treated
with 600 mg/12 mg combination therapy. A reduction in
diastolic BP is consistent with similar observation in

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other troglitazone studies. The direction and
magnitude of the DBP change offers a clinically
desirable endpoint in this population. Given the fact
that hypertensive patients were excluded from this
study, only minor changes would be expected. Since
this study was not powered to detect small changes in
blood pressure, the direction of the observed change
still represents a desirable change in this population.
The reduction in diastolic BP is corroborated by a
decrease in the calculated peripheral resistance in the
subgroup of patients that underwent cardiac output
measurements in this study. This change in BP could
result indirectly from reversing insulin resistance and
amelioration of hyperinsulinemia, or alternatively,
from a direct action of troglitazone on peripheral
vasculature.

Weight
        A statistically significant increase in weight was
observed in the combination arms in contrast to the
troglitazone monotherapy arms in which modest weight
losses of 1 to 7 lbs were seen. While the magnitude of
the change is relatively small (approximately 6%),
minor increases in weight in this population should be
carefully monitored. The fact that weight increases
were observed in the combination therapy arms only and
not the monotherapy arms is suggestive of factors other
than troglitazone therapy being responsible for weight
increases. Several factors may have contributed to
weight gain in this study. The fact that weight gain
was mainly observed in treatment arms associated with
improved glycemic control suggests that diminished
glycosuria may be contributing to weight gain. The
weight increase may possibly be a result of
potentiation of the known affect of sulfonylurea
therapy on weight gain. In addition, patients in this

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study were instructed on a weight maintenance diet for the duration of the study. Appropriate diabetic diet instructions targeting ideal body weight was not implemented in this study. Finally, improving hyperglycemia and achieving target glycemic control in this population is a disincentive to maintain strict caloric and sugar intake. In clinical practice, diet and exercise should be strongly emphasized to avoid potential weight gain.

Safety

Troglitazone, both as mono- and combination therapy, was well-tolerated during the study. The overall adverse event profile of troglitazone/glyburide combination therapy was similar to the adverse event profile of glyburide monotherapy. Most adverse events occurred at the lower incidence in patients treated with troglitazone monotherapy compared with the patients treated with glyburide monotherapy. This may be attributed to a better adverse event profile for troglitazone and may in part be due to the high dropout rate for patients treated with troglitazone monotherapy. Tolerance was also evident by the rare occurrence of unacceptable levels of clinical laboratory parameters; most of these occurrences resolved while study treatment continued.

Summary

In summary, patients with Type II diabetes receiving maximum doses of sulfonylurea have very few oral therapeutic options remaining. Aside from insulin resistance, the hallmark of the disease at this stage is mainly a diminished pancreatic response to glucose stimulus. Improving insulin resistance is of great benefit when added to a current regimen capable of stimulating insulin release (e.g., sulfonylurea).

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Combination therapy of a glitazone and sulfonylurea
appears to be safe and well-tolerated and can result in
significant and synergistic improvement in glycemic
control. It should be noted that patients on maximum
5   doses of a sulfonylurea should not be switched to
glitazone monotherapy. Monotherapy should only be
achieved if indicated by downward titration of the
sulfonylurea dose. Finally, application of the results
of this study should not be limited to patients who
10   fail on maximum doses of sulfonylurea therapy but also
extended to patients on lower doses of a sulfonylurea.

CONCLUSIONS

       Troglitazone/glyburide combination therapy is
15   well-tolerated and significantly (p <0.0001) improves
glycemic control over a 52-week period at doses of
200 mg/12 mg to 600 mg/12 mg compared with glyburide
monotherapy in patients with NIDDM who are not
adequately controlled on sulfonylurea therapy.
20   Additional examples of combination therapy
according to this invention will employ the glitazone
BRL 49653 together with a sulfonylurea selected from
glyburide, chlorpropamide, tolbutamide, and glipizide.
Another combination will be the glitazone TA 174 in
25   combination with a sulfonylurea selected from
glisoxepid, acetohexamide, glibornuride, and
tolazamide. Still another combination provided by this
invention is englitazone together with glibornuride,
glyburide, or glisoxepid. These combinations produce
30   synergistic glycemic control and will be utilized at
doses which are synergistic. The synergistic
combinations of this invention can also be utilized to
treat conditions such as impaired glucose tolerance
(IGT), thereby preventing or delaying the onset of
35   frank NIDDM.

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CLAIMS

1. A composition comprising synergistic effective
    amounts of a sulfonylurea antidiabetic agent and a
    glitazone antidiabetic agent.

2. A composition of Claim 1 wherein the sulfonylurea
    is selected from glisoxepid, glyburide,
    acetohexamide, chlorpropamide, glibornuride,
    tolbutamide, tolazamide, glipizide, gliclazide,
    gliquidone, glyhexamide, phenbutamide, and
    tolcyclamide.

3. A composition of Claim 2 wherein the glitazone is
    selected from troglitazone, ciglitazone,
    pioglitazone, englitazone, TA 174, and BRL 49653.

4. A composition of Claim 3 employing troglitazone
    and glyburide.

5. A method of treating diabetes by administering to
    a patient in need of treatment an effective amount
    of a sulfonylurea antidiabetic agent in
    combination with an effective amount of a
    glitazone antidiabetic agent.

6. A method according to Claim 5 wherein the
    sulfonylurea antidiabetic agent is selected from
    glisoxepid, glyburide, acetohexamide,
    chlorpropamide, glibornuride, tolbutamide,
    tolazamide, glipizide, gliclozide, gliquidone,
    glyhexamide, phenbentamide, and tolcyclamide.

7. A method according to Claim 6 wherein the
    glitazone antidiabetic agent is selected from

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troglitazone, ciglitazone, pioglitazone,
englitazone, TA 174, and BRL 49653.

8.   A method according to Claim 7 employing a
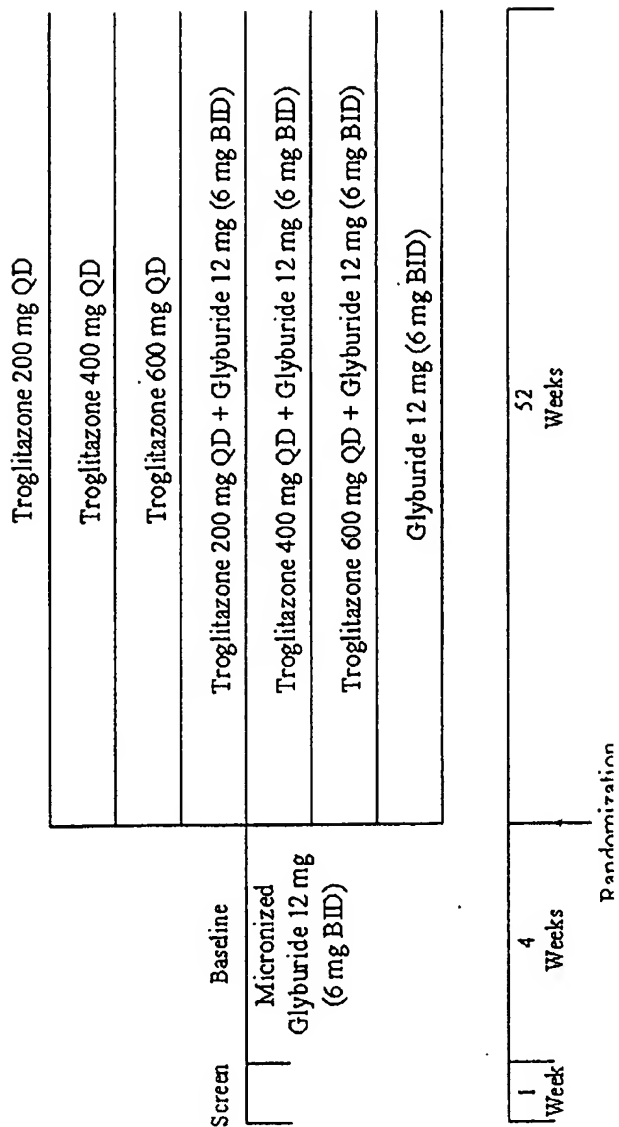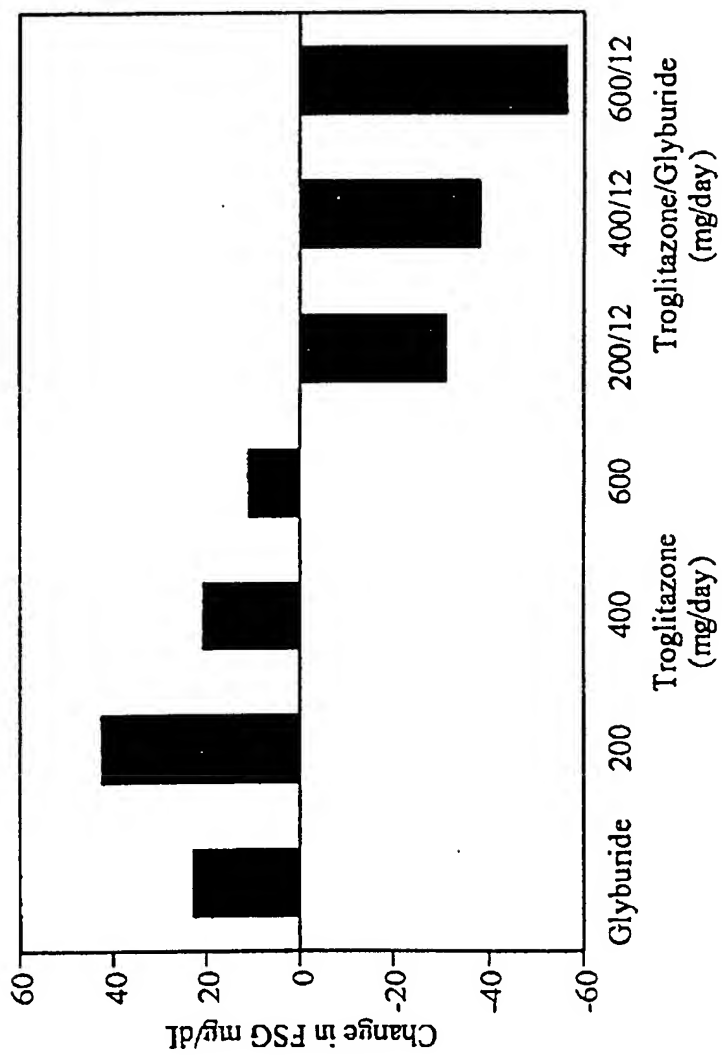   combination of glyburide and troglitazone.

FIGURE 1

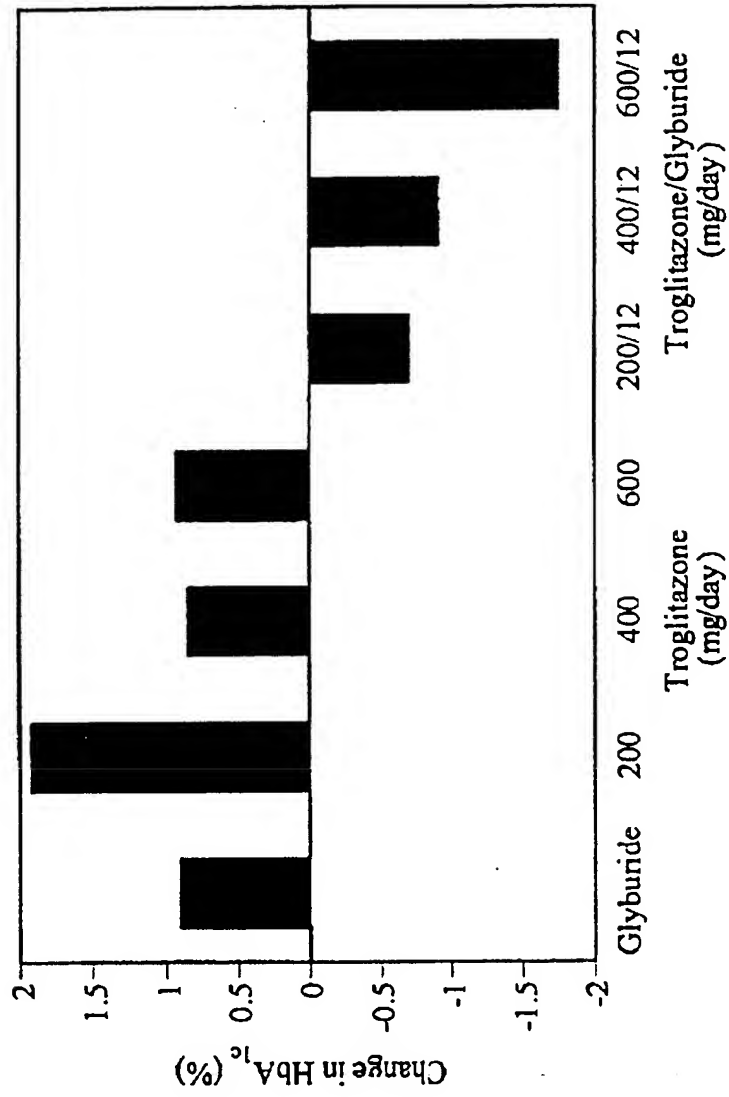FIGURE 2. Mean Change From Baseline in FSG at Week 52 (ITT)

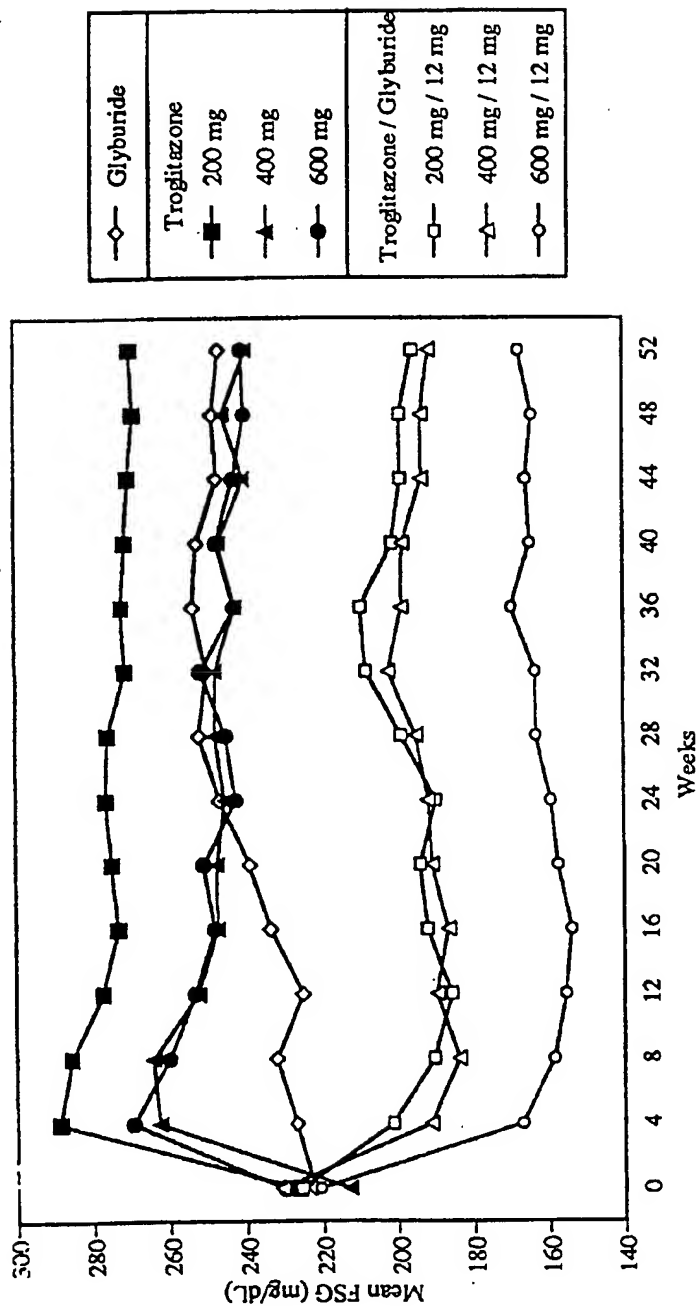FIGURE 3. Mean Change From Baseline in HbA_{1c} at Week 52 (ITT)

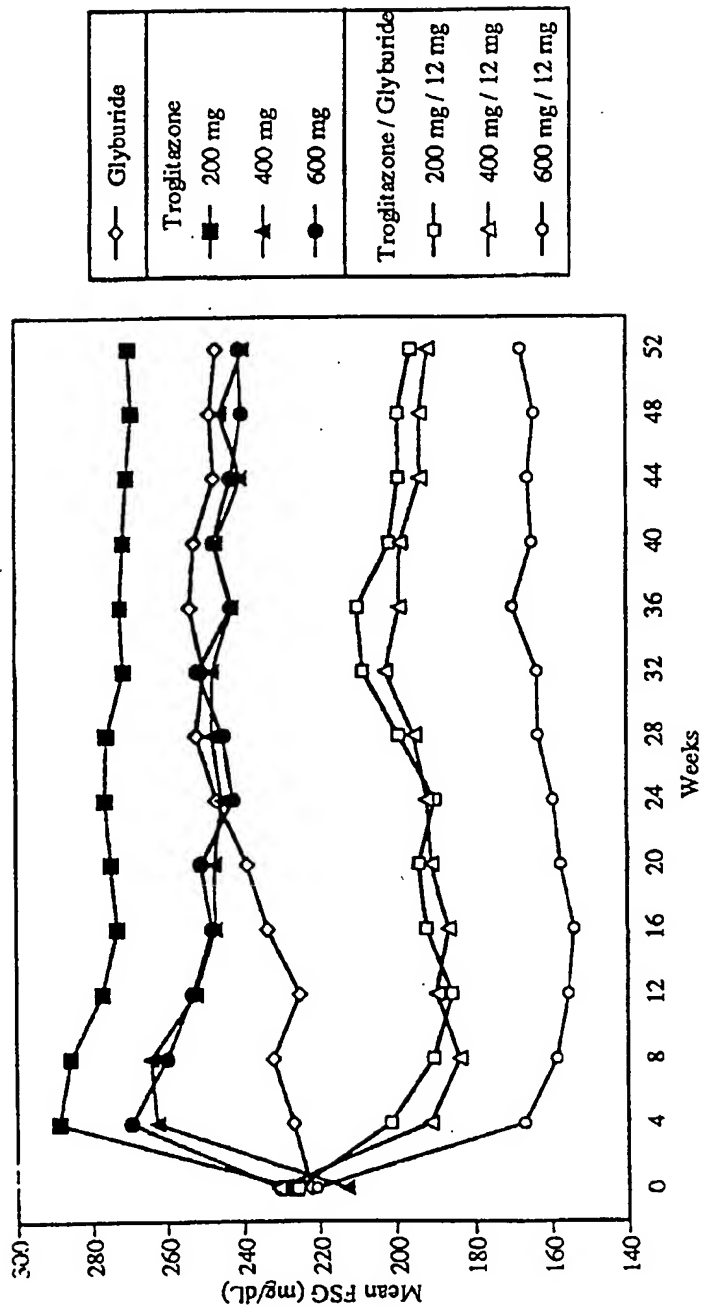FIGURE 4.   Mean Levels of a) FSG and b) HbA$_{1c}$ by Time (ITT)   (Page 1 of 2)

(b)

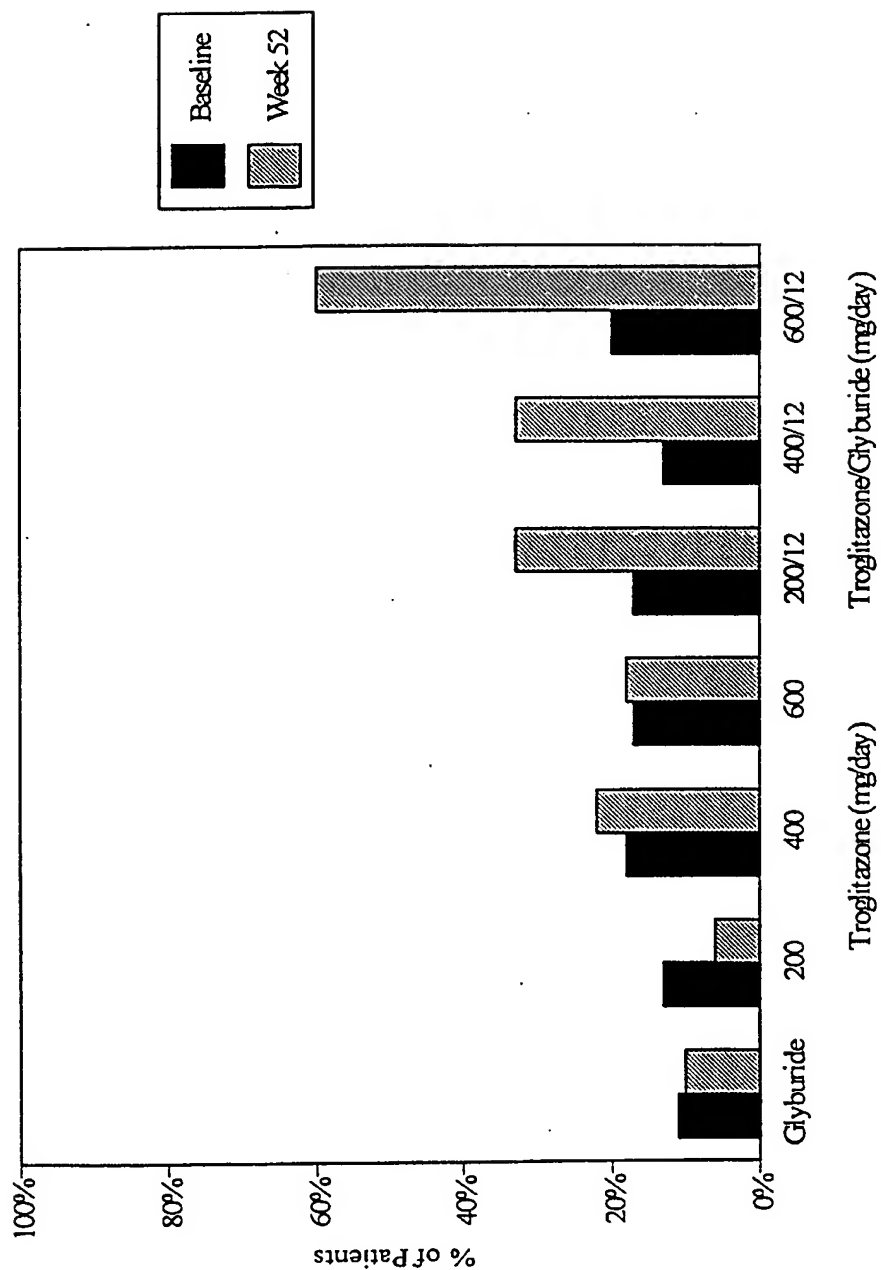FIGURE 4.   Mean Levels of a) FSG and b) HbA$_{1c}$ by Time (ITT)   (Page 2 of 2)

FIGURE 5. Distribution of Patients (%) With HbA$_{1c}$ Level of ≤8% at Baseline and Week 52 (ITT)

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6   A61K31/64   A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6   A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SPENCER ET AL: "Troglitazone" DRUGS, vol. 54, no. 1, July 1997, pages 89-101, XP002064287 see page 91, right-hand column, paragraph 3 - page 93, left-hand column, paragraph 1 ---	1-8
P,X	YAMASAKI ET AL: "Pioglitazone (AD-4833) Ameliorates Insulin Resistance in Patients with NIDDM" THE TOKOHU JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, no. 3, - November 1997 pages 173-183, XP002064288 see abstract see page 175-176 --- -/--	1,3,5,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 1998	2 7. 05. 98

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	IWAMOTO ET AL: "Effect of Combination Therapy of Troglitazone and Sulphonylureas in Patients with Type 2 Diabetes Who Were Poorly Controlled by Sulphonylurea Alone" DIABETIC MEDICINE, vol. 13, no. 4, April 1996, pages 365-370, XP002064289 see page 365, right-hand column, line 5-8, paragraph 2 see page 366, left-hand column, paragraph 1-2 see page 369, left-hand column, line 1-5, paragraph 2	1-8
X	BRESSLER AND JOHNSON: "Oral Antidiabetic Drug Use in the Elderly" DRUGS & AGING, vol. 9, no. 6, 1996, pages 418-437, XP002064290 see page 423, left-hand column, line 8-14, paragraph 4; figures 1,4	1-8
X	EP 0 749 751 A (TAKEDA CHEMICAL INDUSTRIES LTD) 27 December 1996 see page 2, line 39-40; claims 1,14,27 see page 3, line 7-8; claim 10 see page 3, line 49; claim 26 see page 9, line 41-50 see page 4-5	1-3,5,7
X	CHEMICAL ABSTRACTS, vol. 126, no. 20, 19 May 1997 Columbus, Ohio, US; abstract no. 258925, ODAKA ET AL: XP002064292 see abstract & ODAKA ET AL: "Antidiabetic Effects of Pioglitazone.HCl Alone or in Combination with Insulin or Sulfonylurea in Diabetic Animals" YAKURI TO CHIRYO, vol. 25, no. 2, February 1997, pages 345-353, see the whole document	1-3,5-7
X	DE SOUZA ET AL: "Insulin Secretory Defect in Zucker fa/fa Ratsis Improved by Ameliorating Insultin Resistance" DIABETES, vol. 44, no. 8, 1995, pages 984-991, XP002064291 see page 987, right-hand column, paragraph 1; figure 2C; table 3	1-3,5-7

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 09823 A (SHAMAN PHARMACEUTICALS INC) 4 April 1996 see page 21, line 19-25; claims 5,7,8,11 -----	1-8

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Box I   Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:   5-8
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-8 are directed to a method of treatment of the
human/animal body, the search has been carried out and based on the
alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II   Observations where unity of Invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   [ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2179584 A	21-12-96
		CN 1145783 A	26-03-97
		CZ 9601811 A	15-01-97
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